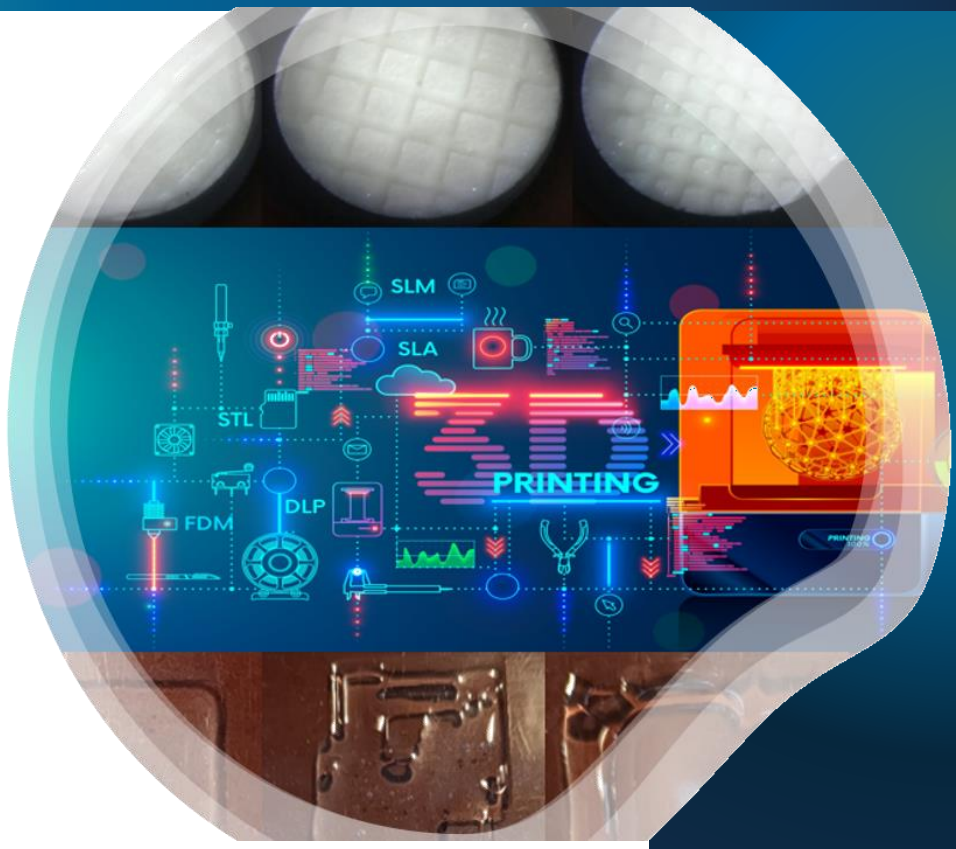
HELLENIC REPUBLIC
National and Kapodistrian University of Athens
Department of Pharmacy
Sector of Pharmaceutical Technology

Application of 3D Printing and Design of Experiments for the Development of Pharmaceutical Products



ELENI TSINTAVI

ATHENS 2022

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Application of 3D Printing and Design of Experiments for the Development of Pharmaceutical Products

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Chemical Engineer, MSc

A Thesis submitted for the Degree of

Doctor of Philosophy

ATHENS 2022

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Σας ευχαριστώ πολύ!

Athens, July 20th, 2022
Eleni Tsintavi

ABSTRACT

Almost all developed pharmaceutical products are placed on the market into a particular dose that fits the average of the population. Characteristics such as age, race, sex, or weight that can lead to variability in the therapeutic effect are not taken into consideration. This "*one-size fits all*" approach is not suitable for all, especially in the cases of pediatric populations or dosage forms with narrow therapeutic index. Thus, the field of precision medicines, which allows each individual patient to be prescribed with customized dosages and tailored release profiles of suitable pharmaceutical forms is gaining ground.

Pharmaceutical compounding is a methodology followed by the pharmacists in order to produce personalized medicines in pharmacies. However, the quality of the preparation is based on the pharmacist's professional education, professional license, and licensing of the pharmacy's premises. Furthermore, the preparation of galenic products in pharmacies is not harmonized throughout at least the European countries. In contrast to the marketed products, galenic preparations are not tested for their effectiveness, safety, and production method as well as for the validation and cleaning of the equipment or their proper labeling and disposal. Therefore, there are deficiencies in the quality control and assurance of these products.

From all the above it is obvious that the prevailing approach so far has many serious disadvantages in terms of its application in the production of personalized medicinal products, especially when using pharmacologically active substances in low doses with a narrow therapeutic range in groups of patients such as children.

A technology such as 3D printing can potentially overcome these challenges and be a tool allowing easy, flexible, low cost and rapid modification of the dose and release of the active pharmaceutical ingredient according to the patient's needs and can offer the desired therapeutic effect, at the point of need and at the time of need. By simply varying basic parameters in the digital design, product customization can be achieved without the need for complex manufacturing equipment and processes.

The main goal of this project was to demonstrate the applicability of 3D printing technology in the pharmaceutical field for the production of personalized dosage forms at the point of need and when in need, while assuring product quality. The combination of Pharma 4.0 technologies such as 3D printing and Machine Vision, analytical techniques, and Quality by Design showed that precision medicines can be manufactured on demand and at the same time assuring both quality and traceability during the whole production process.

The experimental scheme consisted of firstly employing the 3D Printing technology for the partial coating of matrix tablets with glycerides, where the active ingredient release would be precisely regulated by controlling the coating characteristics only, without modifying the core formulation. The feasibility of the proposed technology was shown by modifying the geometry of the coating and acquiring knowledge on which of these parameters and/or their interactions affect the release profile of the active ingredient and thus achieving personalized drug release rates according to the patient's needs.

Secondly, a reliable, flexible, cost-effective and most of all patient-centered system to assure quality when preparing pharmaceutical products in pharmacies and thus mitigating the risks associated with healthcare-medication errors has been developed. The system designed is in line with the most recent regulatory directives incorporating Industry 4.0 key enabling technologies and enables the production of personalized medicinal products at the point of need with the use of 3D Printing, while a combined Deep Neural Network based Machine Vision system and analytical methodology assure both quality and traceability during the whole production process.

The results revealed that 3D printing technology could be employed for addressing the challenges associated with the production of personalized medicine. Through 3D printing flexibility, cost effectiveness, robustness, versatility, precision, and speed, new possibilities to product development and manufacturing were possible.

Keywords: Three-Dimensional Printing, Pharma 4.0, Personalized medicine, Quality by Design, Pharmaceutical Compounding, Deep Neural Networks, Machine Vision.

DOCTORAL THESIS OUTLINE

In Section I.1, the background of the thesis is explained, by giving information about the fundamentals of Industry 4.0 and 3D Printing Technology as a tool of this wave of changes. Furthermore, the application of 3D Printing in the pharmaceutical field is presented by outlining the most recent advances in the relevant research field.

In Section I.2, the theoretical background of Quality by Design is presented. The ICH guidelines related to Pharmaceutical Development, Quality Risk Management and Pharmaceutical Quality System are analyzed in respect to pharmaceutical quality. Moreover, the fundamentals of Experimental Design are shown, the terminology and methodology that follows as well as its basic types. Finally, a comparison between Experimental Design and Traditional Experimental Methods is outlined.

In Section I.3, the need of customization of the different pharmaceutical forms is shown in combination with the process of compounding and the limitations of such processes and how 3D Printing Technology could be a solution.

In Section I.4, the purpose and objective of the PhD thesis is shown by presenting the application of 3D printing in two main pillars, named “Partial Tablet Coating by 3D Printing” and “3D Printing and Machine Vision Application for Quality Risk Management in Compounding Drug Products at the Point of Need”.

In Section II, the experimental methodology used is described in detail with schematic representation of the sequences followed. Also, information about the materials, equipment and experimental conditions are provided in this section.

In Section III, the results from each main pillar are presented. The experimental design results, basic figures and most important tables are included as well. However, the rest of the material can be found in the Appendix. Also, all results presented are evaluated and analyzed.

In Section IV, the general overview of the thesis is made, and conclusions are drawn based on the observed results.

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APPENDIX **I**

I.1. 3D PRINTING & INDUSTRY 4.0

I.1.1. The definition of 3D Printing

Three-dimensional printing (3DP) is a layer-by-layer production of 3D objects from digital designs. The general term 3DP includes a range of different printing technologies according to the raw materials used or the way layers are deposited in order to create the objects. Fused Deposition Modeling (FDM), inkjet printing, stereolithography (SLA) or semisolid extrusion are some examples of 3DP. According to Ventola "*3DP or Additive Manufacturing (AM) or Solid Free-Form (SFF) or Rapid Prototyping (RP) is a manufacturing method in which objects are created by fusing or depositing materials in layers to produce a 3D object*" (Ventola, 2014). ISO/ASTM have defined 3DP as *'Additive manufacturing is the general term for those technologies that based on a geometrical representation creates physical objects by successive addition of material'* or *'the process of joining materials to make parts from 3D model data, usually layer upon layer, as opposed to subtractive manufacturing and formative manufacturing methodologies'* (ISO/ASTM International, 2015). Synonyms of 3DP include additive manufacturing, rapid prototyping, additive fabrication, additive processes, additive techniques, additive layer manufacturing, layer manufacturing, and freeform fabrication (ISO/ASTM Internarional, 2013). All these approaches, despite the type of the 3DP technology, the various operating conditions, the materials used or the differences in speeds and resolution, can construct any 3D model derived from a computer-aided design software (CAD). In other words, 3DP is an additive technology where an object is built according to a digital model through which commands are given to the printer to build the set object layer after layer (Mills, 2015).

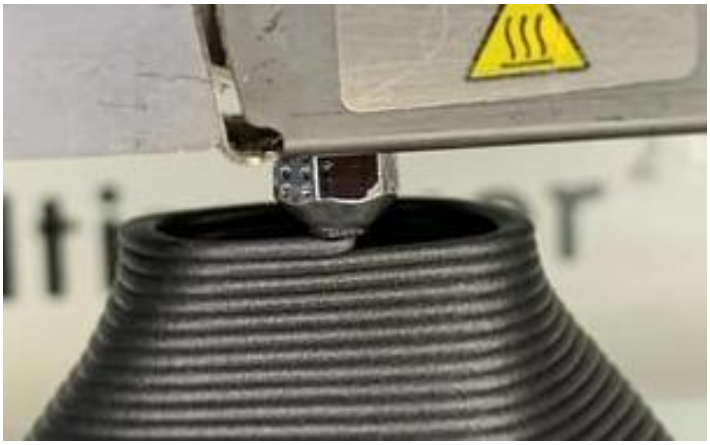


Figure I.1.1: Layer by layer 3D printing manufacturing (https://www.reddit.com/r/3Dprinting/comments/at1t6g/in_love_with_1mm_layer_height_on_a_desktop_3d/).

In a basic setup, a rapid prototyping stereolithography (.stl) file format is created defining the surface geometry of the 3D object (Jonathan and Karim, 2016). In practice, the .stl file gives three sets of coordinates assigned to a vector that essentially constitute the vertices of a triangle and the direction perpendicular to it. Subsequently, through a computer software, a machine specific code (.gcode) is generated from the previously created .stl file, which is read and followed by the 3D printer. This file describes the coordinates the printing head follows, which constructs the object layer by layer by moving the print head along the x-y axis and vertically along the z-axis, as guided by the CAD (Giannatsis and Dedoussis, 2009; Gibson et al., 2015).

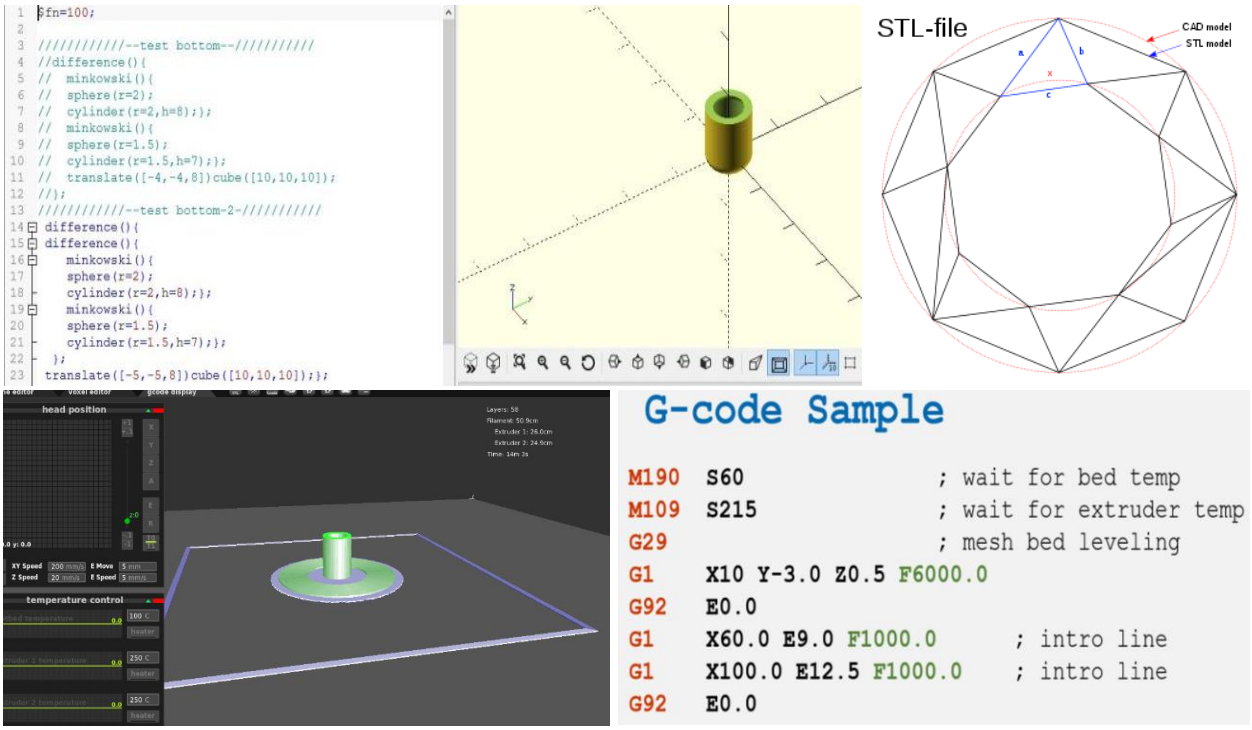


Figure I.1.2: The process of 3DP through CAD: The object is designed (top left), then the .stl file is created describing the surface geometry of the object (top right), transferred to the 3D Printer software (bottom left) in order to generate the .gcode file (bottom right).

The STL file format has its origins from stereolithography but has been established in all additive manufacturing technologies. It is a system-neutral data format for describing only surface geometry of a three-dimensional object as a tessellation of triangles without any representation of color, texture or other attributes and can be stored using either ASCII or binary representations (ISO/ASTM International, 2021).

3D printing requires a large number of instructions for printing. This involves separating an object into many layers, which is called slicing. This process is an essential pre-manufacturing stage in all additive manufacturing technologies and involves separating the model into several consecutive layers and recording the information contained within each layer. Normally this process is automatically performed by a software, once the necessary parameters (e.g., layer thickness) have been set. Instructions are generated for each layer of the object and stored in a file, such as the GCODE file, which is executed by a 3D printer. GCODE is the most widely used computer numerical control programming language and basically it tells the motors of the printer where to move, how fast to move, and what path to follow. GCODE files are

created by slicing programs that translate CAD drawings into G-Code, which a 3D printer can read, and each line represents a different command (ISO/ASTM International, 2021).

I.1.2. Historical Background of Additive Manufacturing

Even though 3D Printing is considered as a new and innovative technology, its history goes back even to the 1940s. The general concept of 3D Printing was first described in science fiction stories back in the 1940s and 1950s by Murray Leinster (*'Things Pass By'*, 1945) and Raymond F. Jones (*'Tools of the Trade'*, 1950). In 1971, Johannes F. Gottwald patented the Liquid Metal Recorder, (U.S. Patent 3596285A), a continuous inkjet metal material device to form a removable metal fabrication on a reusable surface for immediate use. This appears to be the first patent describing 3D printing with rapid prototyping and controlled on-demand manufacturing of patterns. In 1974, David E. H. Jones mentioned the concept of 3D printing in his regular column '*Ariadne*' in the journal New Scientist (Ellam, 2019; Jones, 1974).

In practice, 3D Printing developing started in the 1980s. In April 1980, Dr. Hideo Kodama of Nagoya Municipal Industrial Research Institute invented two additive methods for fabricating three-dimensional plastic models with photo-hardening thermoset polymer, where the UV exposure area is controlled by a pattern or a scanning fiber transmitter (Kodama, 2014). He filed a patent for this invention, which was published on 10 November 1981 (JP S56-144478). His research results were published in April and November in 1981 (Kodama, 1981a, 1981b) and was the first literature to describe the layer-by-layer approach. However, his research was not highly evaluated, and Dr. Kodama did not fulfil the patent rights and was never granted the patent (3DSOURCED, 2022).

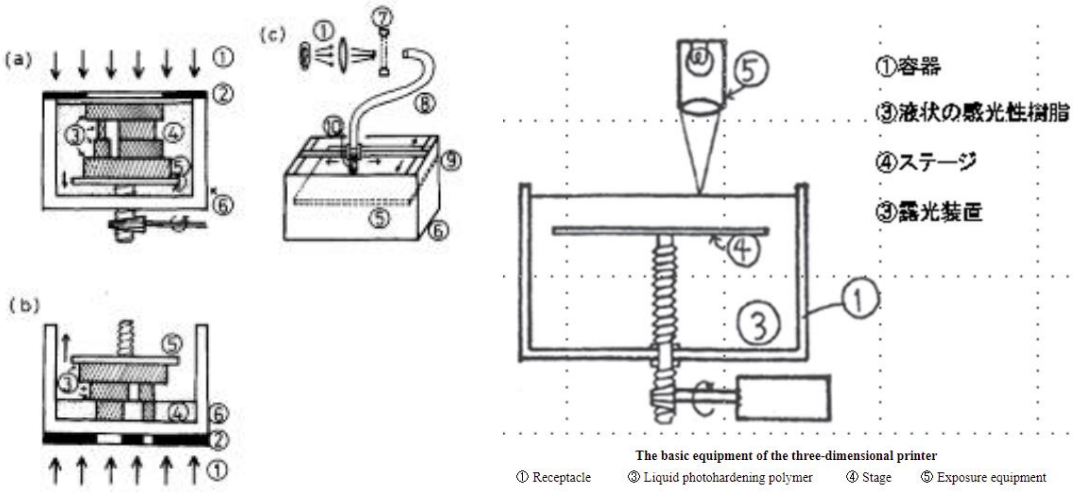


Figure I.1 3: Additive manufacturing by H. Kodama in 1981 (Kodama, 1981a, 1981b)

Later in the 1980s, three French engineers, Alain Le Méhauté, Olivier de Witte, and Jean Claude André filed a patent in 1984 on the Stereolithography process, which they abandoned soon as they claimed "*lack of business perspective*" (3DSOURCED, 2022). Few weeks after the French engineers, Charles 'Chuck' Hull filed his patent (US4575330) for Stereolithography fabrication system, with new features such as the stl file format and digital slicing. In this system, individual layers are added by curing photopolymers with ultraviolet light. Hull defined the process as a "*system for generating three-dimensional objects by creating a cross-sectional pattern of the object to be formed*" (US4575330-Hull, 1986). In 1986 Charles 'Chuck'

Hull was granted the patent and formed the company 3D Systems Corporation, which released the first commercial 3D printer SLA-1 in 1988(3DSOURCED, 2022).

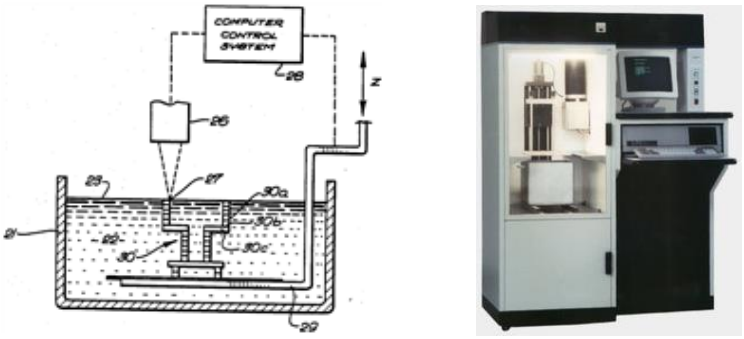


Figure I.1.4: Stereolithography by Chares 'Chuck' Hull in 1986 - US4575330 (Hull, 1986) (left) and the first commercial 3D printer SLA-1 (https://www.3dsystems.com) (right).

In 1988 another 3D printing technology, Selective Laser Sintering (SLS), was created by Carl Deckard at the University of Texas, who filed a patent for this system (US4938816-Deckard and Beaman, 1990). This technology uses a laser instead of UV light to solidify layers of powder polymers. It was then leased to DTM Inc for use.

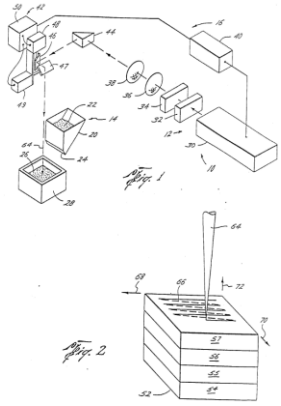


Figure I.1.5: SLS by Carl Deckard in190 – US4938816 (Deckard and Beaman, 1990)

The most common used today 3D printing technology is the Fused Deposition Modelling (FDM) which was developed in 1988 by S. Scott Crump, who filed a patent in 1989 (US5121329-Crump, 1992) and marketed this technology by his company Stratasys in 1992.

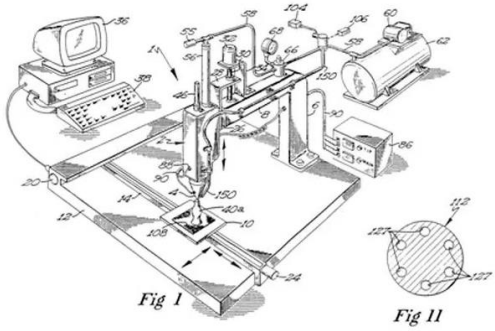


Figure I.1.6: FDM by Scott Crump in 1992 – US5121329 (Crump, 1992).

Dr. Hans Langer founded the company EOS during 1989 in Germany, which dominated the SLS 3D printer market and in the mid-1990s became a pioneer in Direct Metal Laser Sintering. In 1991, after the release of SLA-1, Stratasys released their first FDM 3D printer, being the first real competitor of 3D Systems. The next year in 1992, DTM Inc. released their first SLS 3D printer (3DSOURCED, 2022).

By the mid-90s, new techniques for material deposition were developed at Stanford and Carnegie Mellon University, including microcasting and sprayed materials. Support materials had also become more common, enabling new object geometries. In 1993, Emanuel Sachs at MIT developed a 3D printing technique based on inkjet printers, a technology today known as binder jetting, which was commercialized by Z Corporation, releasing the ZCorp Z402. This model used starch and plaster-based powder materials and a water-based binder to print objects (Sachs et al., 1993).

In 1993 a new inkjet 3D printer company initially named Sanders Prototype, Inc and later named Solidscape was formed, introducing a high-precision polymer jet fabrication system with soluble support structures, (categorized as a "dot-on-dot" technique). Solidscape released the Model Maker in 1994, their first wax 3D printer, one of the most popular models for creating 3D printed jewelry.

Dr. Behrokh Khoshnevis, an academic based in California, was the first to envision in the mid-1990s, industrial-scale printers for creating airplane parts. However, his vision encountered many drawbacks and in 1994 came up with the idea of "*Contour Crafting*" for creating shelters (houses), which he patented in 1996 (Khoshevis, 1996). In 1995 the Fraunhofer Society developed the selective laser melting process.

The late 1990s was another promising era for 3D printing. In 1997 a company named Arcam was created, which specialized in metal 3D printer machines, and which is the only manufacturer of Electron Beam Melting (EBM) 3D printers. Aeromat also this year produced the first 3D printed metal process using laser additive manufacturing (LAM) that utilizes high-powered lasers to fuse powdered titanium alloys (Gonzalez, 2020). Additionally, in the following year, Objet Geometries was established in Israel, which introduced PolyJet 3D printing technology.

In 1999, 3D printing was also introduced to the medical field. Scientists from the Wake Forest Institute for Regenerative Medicine managed to 3D bioprint synthetic scaffolds of a human bladder, which were then coated with cells from the patient's tissue and then were implanted to the patient. This was the first step for the introduction of 3D printing in medicine (3DSOURCED, 2022).

In 2000 the two major companies of the 3D printing field, ZCorp and Object Geometries released their first multicolor 3D printer and inkjet 3D printer respectively. In April 2001, 3D Systems acquired DTM, making it the leader in two 3D printing technologies, SLA and SLS. 2002, was also a major year in bioprinting, as a 3D printed miniature of human kidney was created by Wake Forest Institute for Regenerative Medicine, showing the potential of 3D biopriting in solving the shortage of organs for transplants. The company Envision TEC was then established in 2002, which became a major 3D printing company in jewelry, bioprinting and dental industries.

In 2004 and 2005 the RepRap movement was created. RepRap or '*replicating rapid prototyper*' was launched by Dr. Adrian Bowyer at the University of Bath, who realized that 3D printers could self-replicate, meaning building more versions of themselves. This project from Bath University was open sourced and focused on spreading the low-cost 3D printing worldwide (All3DP, 2016).

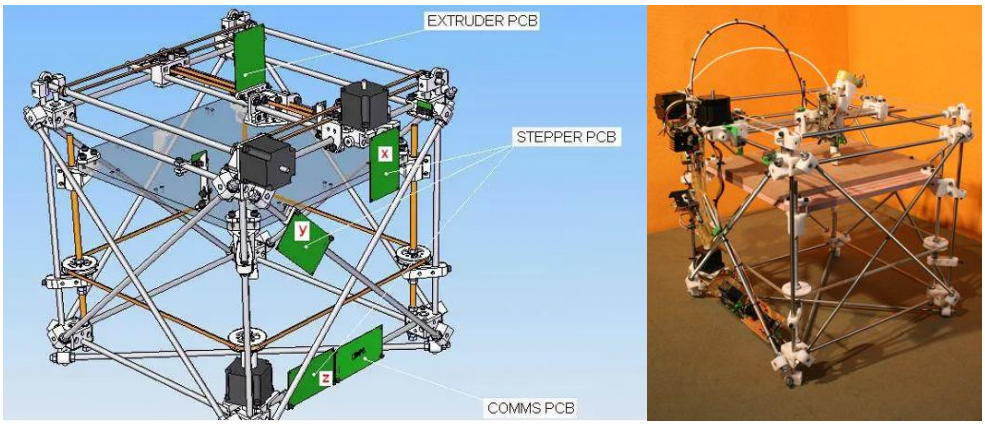


Figure I.1. 7: The first RepRap machine that could self-replicate (3DSOURCED, 2022).

Another major step in 3D printing was made in 2005 as ZCorp released their Spectrum Z510 3D printer, which had the ability not only to print in color, but print in color in HD. Also in this year, ExOne company was established, which later became a leader in binder jetting 3D printing, launching its 3D printers which could 3D print objects in full-color and with very complex geometries not only in metal but in sandstone as well (3DSOURCED, 2022).

In 2008 the RepRap movement became gigantic with the release of the 'Darwin', a printer which could self-replicate and people with moderate technological and technical knowledge could now easily and cheaply 3D print at home. The industrial room-sized machines transformed to home shelf-sized, do-it-yourself (DIY) machines. After this revolution, also in 2008 a small then website called Thingiverse was launched by Makerbot company. In this website, designers were able to upload 3D printer models built on various 3D software for others to download for free and print at home. This website became one of the most popular websites worldwide (Rosen, 2012).

Another revolution that took place in 2008 was the first 3D printed prosthetic(3DSOURCED, 2022). This achievement revealed to the world the full potential of 3D printing, as in combination with 3D scanners, a patient's arm or leg can be scanned and immediately begin to create a prosthetic that fits the patient perfectly. Thus, 3D printing showed that new objects can be built on-demand, customized to the patient's needs and without the need of assembling. Nowadays, this idea is realized by a project called 3-Nable, which encourages people to 3D print for free low-cost prosthetics such as upper-limb devices, fingers or hands, and to develop and improve existing prosthetic models (E-Nable, 2022). Finally, Stratasys released a new biocompatible material for FDM 3D printers, opening the door for 3D bioprinting to become widely available.

In January 2009, after the fall of Stratasys patent for FDM 3D printing, the first affordable FDM 3D printer kit was released, named BfB RapMan. Makerbot company released the first DIY printer kit later in April 2009, which could be built entirely from parts freely available from Thingiverse. Makerbot was becoming the leader of affordable desktop 3D printers. The same year, Organovo, a 3D bioprinting firm, managed to create the first 3D printed blood vessels with a new 3D bioprinter, showing a promising future for printing whole organs such as kidneys and hearts.

Figure I.1 8: The first 3D printer kit – BfB RapMan (Left) and the first DIY 3D printer by Makerbot – Cupcake CNC (Right) (3DSOURCED, 2022).

In 2010, many companies such as Shapeways, Sculpteo, i.materialise and 3D Hubs, offered 3D printing services, meaning that customers could upload a design online and the company would print it and deliver it to them. i.materialize in 2011 was the first to offer 14k gold and sterling silver as 3D printing material, revolutionizing the 3D printed jewelry field. Also in 2011 the first 3D printed car was produced by Kor Ecologic, called Urbee, while in University of Southampton, UK the first unmanned 3D printed aircraft was created (Gonzalez, 2020). Later this year, Ulimaker was established in Netherlands, releasing the first 3D printer made by laser-cut plywood.

Figure I.1.9: The first 3D-printed car – Urbee (left)(https://3dprint.com) and the first Ulimaker 3D printer made by laser-cut plywood (right) (3DSOURCED, 2022).

In 2012, after the expiration of the Stereolithography patents, the first affordable SLA 3D printed was released, named B3Creator. This type of printer utilizes a similar technology to Stereolithography, called Digital Light Processing (DLP), which uses instead of a single UV laser point, a whole layer projection. Six months later, Formlabs launched their first affordable SLA printer and became one of the leading companies in SLA 3D printing.

Figure I.1.10: The first SLA 3D printer by Formlabs – Form I. (Review: Formlabs Form 1 | WIRED by Ariel Zambelich)

In 2012, Stratasys merged with Object Geometries and in 2013, Stratasys also acquired Makerbot, one of the leaders in FDM 3D printing. In 2013, 3D Systems bought the metal 3D printing French company Phenix Systems, making in one of the few large companies dominating in metal 3D printing, along with EOS, Arcam and SLM Solutions (3DSOURCED, 2022).

In 2014, NASA announced that they used a 3D printer in space, opening the door for future space manufacturing and the ability of future astronauts to create tools on-demand in space (Hubscher, 2014). Also in 2014, the major SLS patent expired, thus companies like Sintratec and Formlabs started working on creating cheaper alternatives.

By that time, many 3D printing companies creating affordable machines antagonized industrial 3D printers and lead companies such as 3D Systems and Stratasys. Examples include Ultimaker, Lulzbot and Prusa 3D printers in the desktop and DIY 3D printer kit markets, Desktop Metal, Markforged, and Carbon 3D in the industrial sector.

Carbon 3D was created in 2014 by Joseph and Philip DeSimone in California, having a new technology called CLIP, Continuous Liquid Interface Production, which could print 100 times faster than other 3D printing technologies, making them able to antagonize technologies such as injection molding and other processes for large-volume plastic parts (Desimone et al., 2014). Like Carbon 3D, in 2015 Desktop Metal was founded, inventing a new technology called Bound Metal Deposition, similar to FDM but working with metal instead of plastic. Their metal 3D printers can print metal 10 times cheaper than alternative printers. Another technology by Desktop Metal is the Single Pass Jetting, a new type of binder jetting technology that is able to build metal parts in minutes rather than hours as with Direct Metal Laser Sintering, making it a revolutionary technology.

Figure I.1.11: CLIP technology by Carbon 3D (left),Bound metal deposition 3D printer Studio System™ 2 Printer by Desktop Metal (middle) and Single pass jetting 3D printer P-50 by Desktop Metal (right) (3DSOURCED, 2022; Desktop Metal. Define the future. Make it real. | Desktop Metal).

In 2015, Cellink, a Swedish company, introduces the first standardized commercial bio-ink to the market derived from a seaweed material called non-cellulose alginate. The bio-ink can be used for printing tissue cartilage. Later in the year, Cellink releases the INKREDIBLE 3D printer for bioprinting services, creating an affordable market for bioprinting (Gonzalez, 2020).

In 2016, two giant technology companies, HP and GE entered the 3D printing market. HP, a leader in inkjet 2D print, announced the release of 3D printers with their patent technology Multi Jet Fusion (MJF), which was realized in 2018, with full-color 3D printers. GE in 2016 acquired the metal 3D printing companies Arcam and Concept Laser. In the same year, Ultimaker released a 3D printer landmark, the Ultimaker 3, while remaining committed to the open source philosophy.

Figure I.1.12: Ultimaker 3, a landmark in 3D printing (3DSOURCED, 2022).

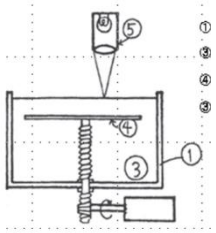
In the construction sector, in the period of 2016-2018, companies such as Apis Cor. and WinSun created huge concrete 3D printers for the construction of skeletons of houses in a quicker and cheaper way. Apis Cor. managed to 3D print a hole house in just 24 hours, while in Dubai, bridges, house and planes or skyscrapers are 3D printed. Apis Cor. Also, in 2019 built the world's largest 3D printed building in Dubai.

Figure I.1.13: 3D printed house by Apis Cor. (apis-cor.com)

In the resin 3D printing technology, the LCD 3D printing technology would change things, as it was a new low-cost technology similar to DLP and simpler than SLA. The cost of this type of printers was reduced dramatically. Examples of LCD printers are the ELEOO Mars and AnyCubic Photon.

Figure I.1.14: The ELEGOO Mars (left) and AnyCubic Photon (right) are two low-cost LCD printers (3DSOURCED, 2022).

Today, additive manufacturing is a mature technology. It is believed that traditional CNC and milling manufacturing will be replaced in the near future and is predicted that by 2030, 3D printing will be worth $51 billion (Redshift Autodesk, 2021). Everything can be 3D printed from food to human organs and buildings, making 3D printing applicable to many sectors such as construction, medicine, product design and manufacturing, aerospace, electronics, jewelry, and pharmaceutics. With new research and developments in additive manufacturing on the rise, the future remains bright for 3D printing.

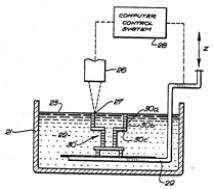


1980

Hideo Kadama files the first 3D printing patent application, describing a photopolymer rapid prototyping system that uses UV light to harden the material. The idea is never commercialized.

1983

Charles Hull invents the first stereolithography apparatus (SLA) machine

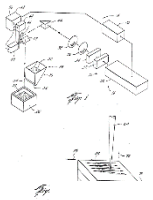


1986

Charles Hull is granted the first patent in 3D printing for an SLA machine. Charles goes on to co-found 3D system Corporation.

1987

Carl Deckard files a patent for a selective laser sintering (SLS) process. The patent was issued in 1989 to DMT Inc., a company later acquired by 3D Systems.



1988

3D Systems sells the first commercial rapid prototyping printer, the SLA-1.

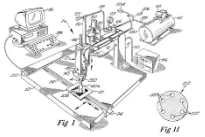
1989

Scott and Lisa Crump file for a patent for fused deposition modeling (FDM) . Scott Crump would go on to co-found Stratasys Inc.

Hana Langer establishes EOS GmbH in Germany and becomes an industry leader in laser sintering

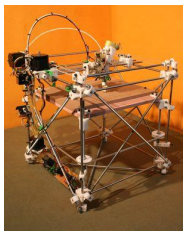
1997

Aeromat produces the first 3D printed metal process using laser additive manufacturing (LAM) that utilize using high-powered lasers to fuse powdered titanium alloys.



1999

Wake Forest Institute of Regenerating Medicine grows the first 3D printed organ for transplant surgery, a lob-grown urinary bladder.



2005

Dr. Adrian Bowyer invents the RepRap open-source concept to create a shelf-replicating 3D printer process. This opened the doors for the creation of several new 3D printers

2008

“Darwin” becomes the first commercially available 3D printer that was designed under the RepRap concept.

Shapeways launches a 3D printing service that allows users to submit their own files for personal fabrication

2009

The FDM patent previously held by Stratasys expires. The average FDM 3D printer price drops form $10,000 to under $1,000.

Micro, a consumer 3D printer that supported PLA and BS materials, launches a successful Kickstarter campaign becoming the most funded 3D printer project ever on the platform

Makerbot launches and brings 3D printing into the mainstream by introducing do-it-yourself kits for people that want to build their own 3D printers.

Makerbot introduces the Thingiverse file library that allows users to submit and download 3D printable files, becoming the largest online 3D printing community and file repository.

2011

In the UK, the University of Southampton designs and 3D prints the first unmanned 3D printed aircraft.

Kor Ecologic unveils the Urbee, a prototype car with 3D printed body, at the TEDXWinnipeg conference.

2012

B9Creator and Form-1 launch successful Kickstarter campaigns, introducing into the entry-level market alternative 3D printing process: DLP technology and stereolithography respectively.

2013

Stratasys acquires Makerbot for around $400 million.

2015

Cellink, a Swedish company, introduces the first standardized commercial bio-ink to the market derived from a seaweed material called non-cellulose alginate. The bio-ink can be used for printing tissue cartilage.

Later in the year, Cellink releases the INKREDIBLE 3D printer for bioprinting services, creating an affordable market for bioprinting.

2019

With the expiration of patents and open-sourced projects, there are over 170 3D printer system manufacturers across the world. This list includes 3D Systems, Stratasys, Fusion3, Formlabs, Desktop Metal, Prusa and Voxel8, among many others.

Figure I.1.15: The timeline of 3D printing (Gonzalez, 2020).

I.1.3. 3D Printing Technologies

There are various ways to classify the 3D printing processes, according to the additive process followed, the form of the raw materials used, the mechanism of layering, or even the kind of printing heads utilized (Gibson et al., 2015). The following figure illustrates the main technologies categorized by the raw materials employed (Siamidi et al., 2020). Among them, stereolithography (SLA), selective laser sintering (SLS), binder jetting (BJ), and fused deposition modeling (FDM) are the most used in the literature for the production of pharmaceutical dosage forms (Goole and Amighi, 2016).

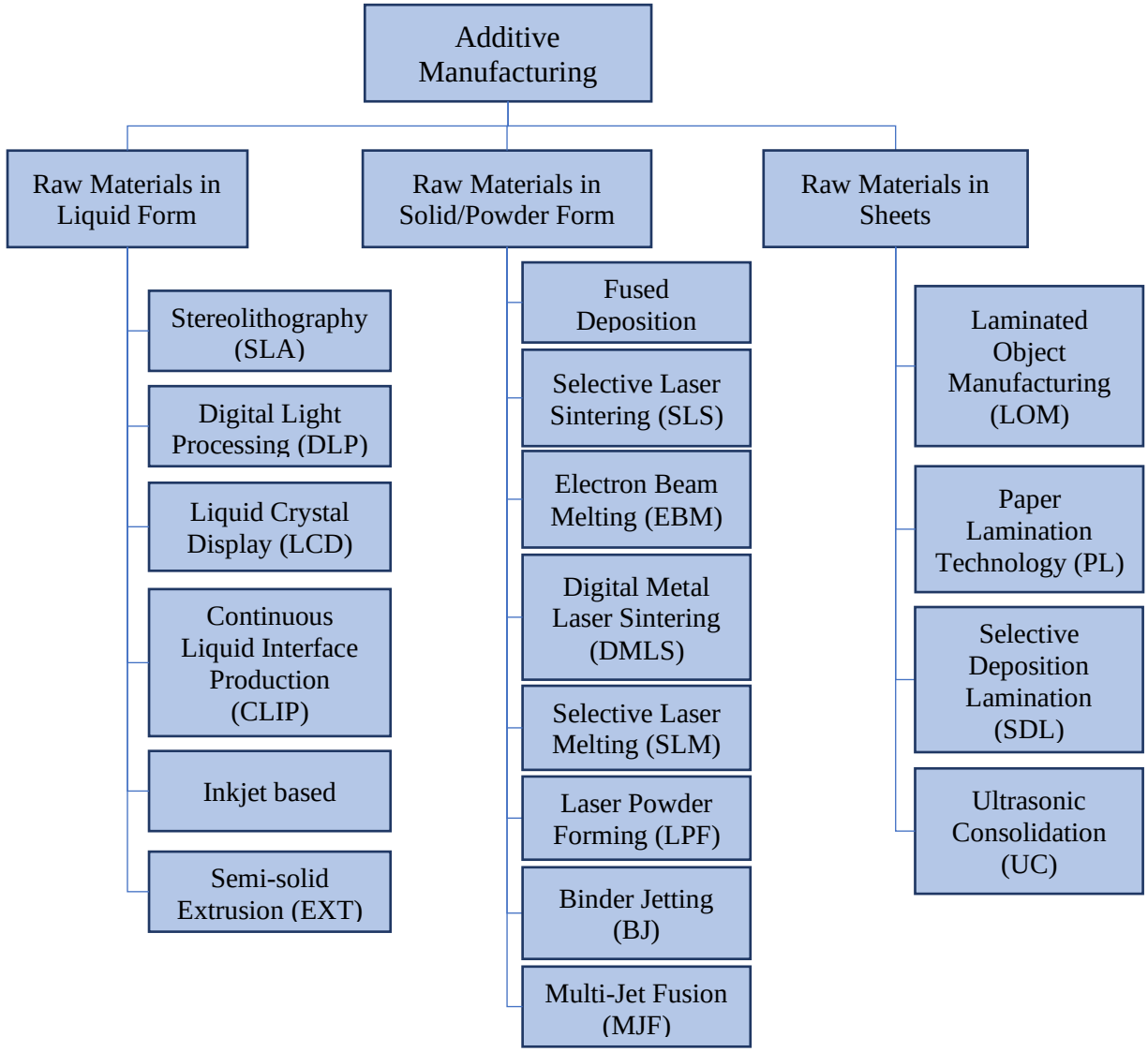


Figure I.1.16: Classification of 3D printing technologies according to the raw materials employed (Siamidi et al., 2020).

A more precise way to classify the various types of 3D printing technologies is according to processes which use a common type of machine architecture and similar materials transformation physics, an approach adopted by the American Society for Testing and Materials International (ASTM) / ISO standards (Alexander et al., 2021; Gibson et al., 2021). This categorization is illustrated in the following table.

Table I.11: Generalized standard terms for 3D printing technologies along with additive manufacturing examples and description (Alexander et al., 2021; ISO/ASTM Internarional, 2013; ISO/ASTM International, 2021, 2015).

Generalized Standard Term	Additive Manufacturing Technique	Description
Material Extrusion	• Fused Deposition Modeling (FDM)/ Fused Filament Fabrication (FFF) • Semi-solid Extrusion (EXT)	Material is selectively dispensed through a nozzle or orifice
Powder Bed Fusion	• Selective Laser Sintering (SLS) • Selective Laser Melting (SLM) • Direct Metal Printing (DMP) • Direct Metal Laser Sintering (DMLS) • Electron Beam Melting (EBM) • Multi Jet Fusion (MJF) • High Speed Sintering (HSS)	Thermal energy selectively fuses regions of a powder bed.
Material Jetting	• Drop-On-Demand (DOD) • PolyJet • ProJet Multijet Printing (MJP) • Nanoparticle Jetting (NPJ)	Droplets of build material are selectively deposited.
Binder Jetting	• Binder Jetting • Color Jet Printing (CJP)	A liquid bonding agent is selectively deposited to join powder materials.
Vat Photopolymerization	• Stereolithography (SLA) • Direct Light Processing (DLP) • Liquid Crystal Display (LCD) • Continuous liquid interface production (CLIP) • Masked Stereolithography (MSLA) • Micro Stereolithography (μSLA) • Programmable Photopolymerization (P3) • High Area Rapid Printing (HARP) • Lithography-based Metal Manufacturing (LMM) • Light Enabled Additive Production (LEAP) • Projection Micro Stereolithography (PμSL) • Digital Composite Manufacturing (DCM)	Liquid photopolymer in a vat is selectively cured by light-activated polymerization.
Direct Energy Deposition	• Laser Engineered Net Shape (LENS) • Electron Beam Additive Manufacture (EBAM) • Cold Spray • Direct Metal Deposition (DMD) • Wire Arc Additive Manufacturing (WAAM) • Rapid Plasma Deposition (RPD)	Focused thermal energy is used to fuse materials by melting as they are being deposited.

Generalized Standard Term	Additive Manufacturing Technique	Description
Sheet Lamination	• Laminated Object Manufacturing (LOM) • Ultrasonic Consolidation (UC) • Selective Lamination Composite Object Manufacturing (SLCOM) • Plastic Sheet Lamination (PSL) • Computer-Aided Manufacturing of Laminated Engineering Materials (CAM-LEM) • Selective Deposition Lamination (SDL) • Composite Based Additive Manufacturing (CBAM)	Sheets of material are bonded to form an object.

Material Extrusion

Material Extrusion is an additive manufacturing process in which material is selectively dispersed through a nozzle or orifice (ISO/ASTM International, 2015). As its name indicates, the object is formed by extruding material layer by layer and depositing it on a built platform. Two are the most common types of material extrusion technologies, Fused Deposition Modeling (FDM) and Semi-solid Extrusion (EXT).

- Fused Deposition Modeling (FDM)

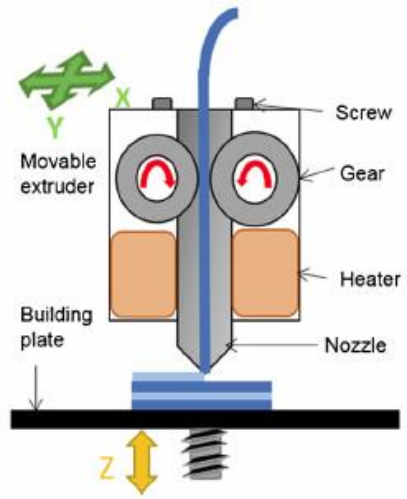


Figure I.1.17: Fused Deposition Modeling (FDM)3D printing technology (Alhnan et al., 2016a).

In Fused Deposition Modeling (FDM) also called Fused Filament Fabrication (FFF) material is extruded through a nozzle. The material is in the form of a solid filament, which is pushed through a heated nozzle, which melts the material in the process. The printhead deposits the material on a built platform along a predetermined path, where the filament then cools and solidifies to form a solid object. The printhead is allowed to move to a three-axis system, in the x-, y- and z- directions, thus forming the three-dimensional object. There are various types of printheads, the ones that are equipped with one nozzle, the ones that two separate nozzles are attached to the same printhead allowing the simultaneous feed of two different filaments as well as the printheads that allow the feed of two different filaments in the same nozzle, thus enabling material mixing. The most common materials used are thermoplastic filaments such as PLA, PVA,

ABS, PET, PETG, TPU, Nylon, HIPS, Carbon Fiber, and ASA, but also metal-filled filaments or wood-filled filaments. This type of 3D printing is the most widely used method as it is cost-effective and with a wide range of materials. Most FDM systems allow for the adjustment of several process parameters. These include the temperatures of the nozzle and build platform, extrusion speed, layer height and cooling fan speed. Common applications include rapid prototyping and product development especially early on for proof of concept, toy manufacturing, automobiles, architecture, detail components and technical manufacturing tools etc. Parts printed with this technology have excellent mechanical strength and heat resistance, allowing their use as functional prototypes. Recently FDM has also been introduced into drug research and development (Alhnan et al., 2016a).

- Semi-solid Extrusion (EXT)

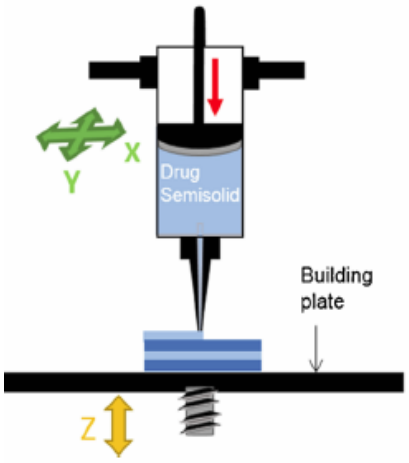


Figure I.1.18: Semi-solid Extrusion (EXT) printing technology (Alhnan et al., 2016a).

A second type of material extrusion additive manufacturing is the Semi-solid Extrusion (EXT). In this type of 3D printing, the object is formed by extruding semi-solids such as pastes, gels or ceramics through a syringe-based precise printhead (Alhnan et al., 2016a). Semi-solids are commonly formulated by dissolving polymers to aqueous or organic solvents in order to obtain gels or pastes of appropriate viscosity that can be loaded to the syringe-type nozzle and be extruded. The printed object can then be dried, and the solid 3D object is obtained. This technology has extensively been used in bioprinting of scaffolds and tissue engineering, in medicine, pharmaceutics, food industry and ceramics, as it does not require high temperatures, the raw materials can be in almost liquid form and complex designs can be formed.

Powder Bed Fusion

Powder bed fusion is an additive manufacturing process in which thermal energy selectively induces fuses between powder particles inside a powder bed to create a solid object layer by layer (ISO/ASTM International, 2015). Powder bed fusion devices spread a thin layer of powdered material over the print bed, typically with a type of blade or wiper. Energy fused specific points on the powder layer, then another powder layer is deposited, and the process repeats until the entire object is fabricated. The final item is encased and supported in the unfused powder. The most common powder bed fusion technologies are Selective laser sintering (SLS), Selective Laser Melting (SLM), Direct Metal Laser Sintering (DMLS) and Multi Jet Fusion (MJF).

- Selective Laser Sintering (SLS)

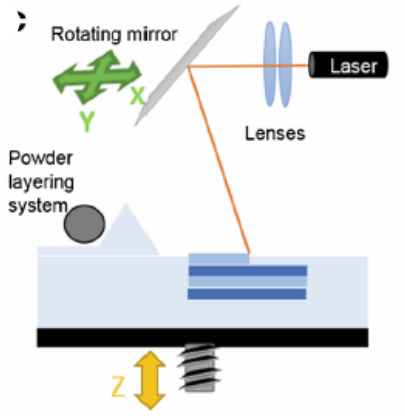


Figure I.1.19: Selective Laser Sintering (SLS) printing technology (Alhnan et al., 2016a).

In SLS, powdered material is heated to just below its melting point and is then spread over the built platform in a very fine layer. A laser or electron beam in then directed across the powder's surface, where it selectively sinters/fuses particles together to form a single cross-section of the print. Subsequently the built platform moves down one layer thickness in height, and a new powder layer is deposited by the powder layering system and the laser will sinter the next cross-section of the object onto the previously solidified cross-sections. The whole process is repeated until the object is fully manufactured. The powder that hasn't been sintered remains in place to support the object, which reduces or eliminates the need for support structures. The powders or starting materials that could be used include polyamides, polystyrenes, or polycarbonates. SLS has been used for the manufacturing of artificial tissue (Alhnan et al., 2016a).

- Selective Laser Melting (SLM) and Direct Metal Laser Sintering (DMLS)

Both technologies produce objects in a similar fashion to SLS. The main difference is that these types of 3D printing technology are applied to the production of metal parts. DMLS does not melt the powder but instead heats it to a point so that it can fuse on a molecular level, thus producing porous metal parts. SLM uses the laser to achieve a full melt of the metal powder forming a homogeneous part. Since this is only possible when the particles have the same melting point, SLM can only print in single metals, not alloys. This is the main difference between DMLS and SLM; the former produces parts from metal alloys, while the latter forms single element materials, such as titanium. Unlike SLS, the DMLS and SLM processes require structural support to limit the possibility of any distortion that may occur (3D Systems, 2022; OpenWorldLearning, 2021).

- Multi Jet Fusion (MJF)

MJF was introduced to the market by HP and even though it has similarities to binder jetting, is a powder bed fusion 3D printing technology and technically produces objects through a combination of SLS and material jetting technologies. More specifically, the printer lays down a layer of material powder on the printing bed and then an inkjet head selectively deposits both a fusing and a detailing agent. Subsequently, an infrared heating unit passes and wherever a fusing agent has been deposited, the underlying layer melts together as the fusing agent improves heat absorption, while the areas with detailing agent remain as a powder. The MJF is faster than SLS as the whole layer is fused at once than a single point (3D Sourced, 2021).

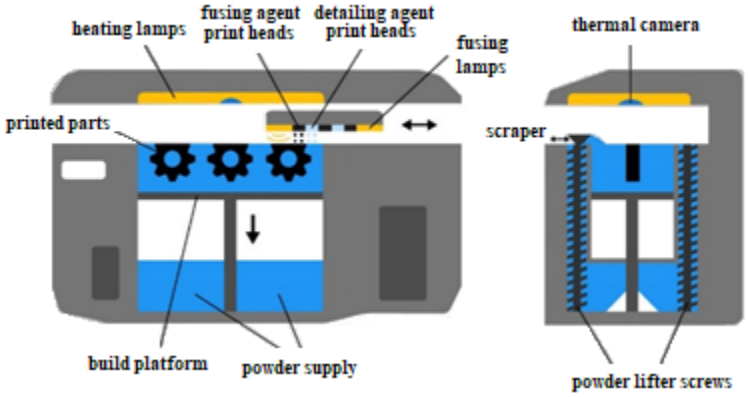


Figure I.1.20: Multi jet fusion (MJF) 3D printing technology (3D Sourced, 2021).

Material Jetting

Material Jetting is an additive manufacturing process in which droplets of build material are selectively deposited (ISO/ASTM Internarional, 2013). This type of 3D printing also known as Inkjet Printing is based on 2D inkjet document printing and includes technologies such as PolyJet from Stratasys Corp., also known as Multijet Printing (MJP) or Multijet Modeling (MJM), Continuous Inkjet (CIJ) or Drop-on-demand (DOD). In these technologies instead of jetting drops of ink onto paper, layers of liquid photopolymer are jetted onto a built tray and are cured with a high-energy light source like UV. This process is repeated layer-by-layer to create the 3D object. Firstly, the liquid goes through an orifice or a nozzle and then in CIJ is pushed through the nozzle continuously and then capillary-driven Rayleigh-Plateau forces break the jet into a stream of droplets. Subsequently, the droplets are charged with field plates and are deflected onto the built tray. On the other hand, in DoD the fluid passing the nozzle is transformed into drops by thermal or piezo-electric actuation (Guo et al., 2017).

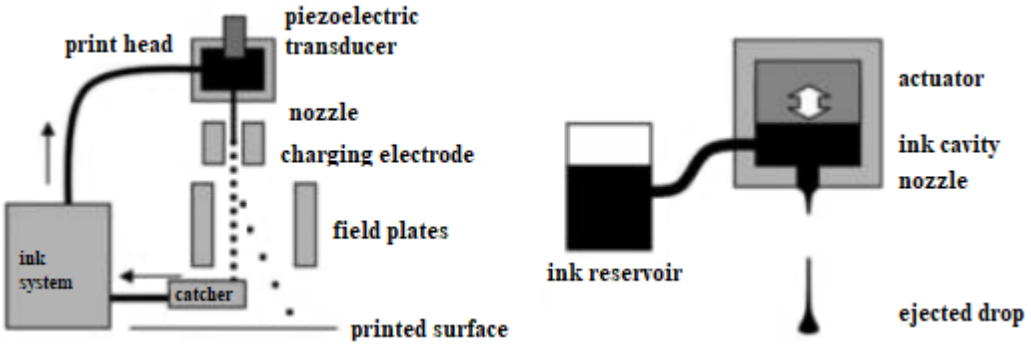


Figure I.1.21: Continuous Inkjet Printing (left) and Drop-on-Demand Inkjet Printing (right) (Guo et al., 2017).

Inkjet printing has many advantages such as high quality and speed, high precision, and can use a wide variety of materials from rubber to rigid and transparent to opaque. It is able to print thin layers, thus making complex designs with fine details and smooth finished surfaces. Examples of materials used in this type of technique are polymers such as poly(3,4-ethylenedioxythiophene), poly(pyrrole), polyaniline, and poly(p-phenylene vinylene), metals such as silver and gold nanoparticle dispersions, silver and gold precursor solutions, graphene, carbon nanotubes and carbon black, ceramics like Alumina, zinc oxide and silicon nitride/oxide and biomaterials such as proteins, DNA, and cells (Guo et al., 2017). Among the disad-vantages of this technology is the poor mechanical properties, consequently the objects are not suitable for

functional prototypes, the lower temperature resistance, and the materials used are slightly more brittle and are not UV-resistant, so fragility and discoloration are possible. Finally, the material cost is higher, and the material variety is limited when compared to other 3D printing technologies.

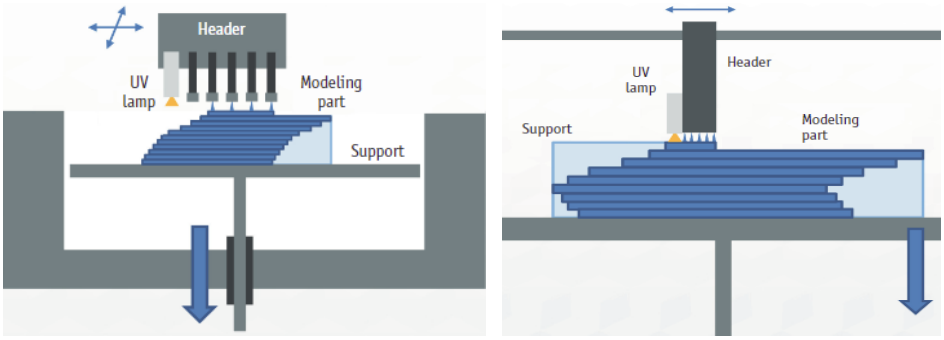


Figure I.1.22:Polyjet 3D printing (left) and Multi-jet modeling 3D printing (right) (Kim et al., 2016)

Binder Jetting

Binder Jetting is an additive manufacturing process in which a liquid bonding agent is selectively deposited to join powder materials (ISO/ASTM Internarional, 2013). Like powder bed systems, binder jetting requires an initial layer of powder on the built platform. Then, a printhead moves over the powder surface depositing binder droplets, which are typically 80 microns in diameter. These droplets bind the powder particles together to produce each layer of the object. Like the other similar systems, once a layer has been printed, the powder bed is lowered, and a new layer of powder is spread over the recently printed layer. This process is repeated until a complete object is formed. It is also possible to print in color with this technology (Alexandrea, 2019).

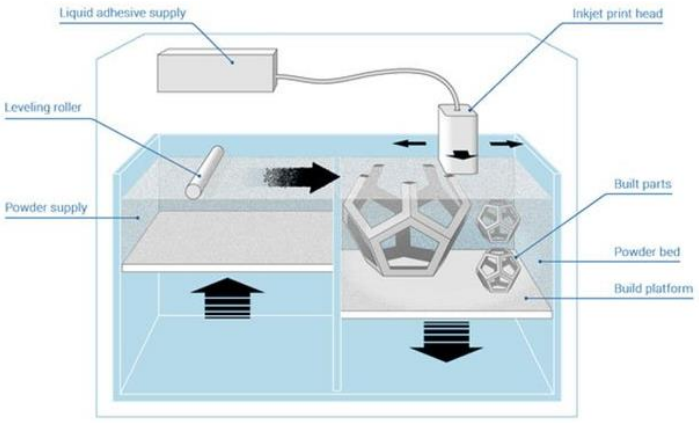


Figure I.1.23: Binder Jetting 3D printing technology (Alexandrea, 2019).

Typical materials used with this technology are polymers, sand, gypsum, ceramic-metal composites, or metal powder. This technique a has been utilized for the fabrication of implants and solid pharmaceutical dosage forms, such as the first commercially printed tablet Spritam® (Alhnan et al., 2016a).

Vat Photopolymerization

Vat polymerization is a 3D printing process where a light source selectively cures a photopolymer resin in a vat. In other words, light is precisely directed to a specific point on a thin layer of liquid photopolymer

to harden it (ISO/ASTM Internarional, 2013). In more detail, a build platform is submerged in a tank that is filled with the resin. The light is selectively directed across the resin surface with mirrors. Once a layer is cured, the platform is raised or lowered a small increment to allow new liquid to flow. The next layer is then cured and adjoins the previously cured one. This process is repeated layer by layer until the 3D part is formed. Common forms of vat photopolymerization are Stereolithography (SLA), Direct Light Processing (DLP), Liquid Crystal Display (LCD) and Continuous Liquid Interface Production (CLIP).

- Stereolithography (SLA)

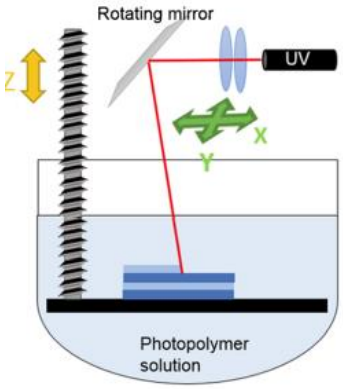


Figure I.1.24: Stereolithography (SLA) 3D printing technology (Alhnan et al., 2016a).

Stereolithography (SLA) employs raw materials in the liquid form, such as photosensitive/ photopolymerizable liquid resins. A high-energy light source like ultraviolet irradiation (UV) solidifies the liquid resins, creating the 3D object layer by layer. SLA uses a single-point laser to trace a thin line along the surface of the resin and includes a mirroring device for the light scattering in order to initiate the gelation process of the photopolymer in the exposed to the light area. Support structures may be utilized in this technique in order to avoid collapse of layers during printing (Pravin and Sudhir, 2018). The liquid polymers used in this type of printing techniques are usually low-molecular weight polyacrylates, epoxy macromers or monomers. Among the advantages of this technique are the high accuracy and good surface quality of the object. This method has been widely used for implant design and manufacture as well as for creating accurate 3D models acquired from various anatomical scans of a patient. On the other hand, some of the disadvantages of this technique is the potential health hazards from the use of resigns and the long-term stability as these resigns are photosensitive (Alhnan et al., 2016a).

- Digital Light Processing (DLP) and Liquid Crystal Display (LCD)

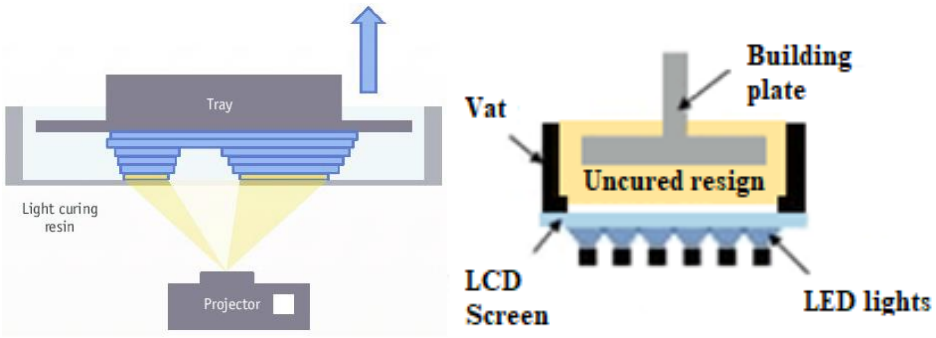


Figure I.1.25: Digital Light Processing (DLP) 3D printing technology (Kim et al., 2016) (left) and Liquid Crystal Display (LCD) 3D printing technology (Mohamed et al., 2019) (right).

Similar to SLA technology are the Digital Light Processing (DLP) and Liquid Crystal Display (LCD) 3D printing technologies. DLP differs from SLA as it uses a digital light projector to project an entire layer instead of a single UV laser point. In order to do so, a digital micromirror device inside the projector lens is used, consisting of numerous tiny micromirrors to reflect the light onto the surface of the liquid resign, and thus controlling the pattern that is printed. Consequently, DLP is faster than SLA. On the other hand, DLP has lower resolution than both SLA and LCD due to the nature of the projector, which is a digital screen composed of square pixels, each pixel size depending on the size of the tiny mirrors, projecting light from a small source to a wider one, distorting its pixels due to spherical aberration. Efforts are made to improve the impact of spherical aberration in the new 3D printers (Lalwani, 2020).

LCD 3D printing technology works in a similar manner with DLP but utilizes LED lights to imprint patterns on the resign surface. This technology offers up to 4K resolution, making LCD 3D printers to approach the accuracy and precision provided by traditional SLA 3D printers (Lalwani, 2020). Apart from increased resolution, another advantage of LCD 3D printers is the increased printing speed when compared to SLA. Finally, LCD 3D printers are more cost-efficient than both SLA and DLP 3D printers. The application of this technology includes medical, dental, aerospace, and automotive industries.

- Continuous Liquid Interface Production (CLIP)

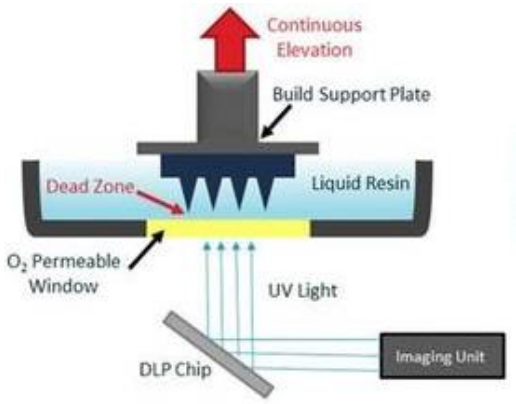


Figure I.1.26: Continuous Liquid Interface Production (CLIP) 3D printing technology (Ogundele and Okafor, 2017).

On an industrial scale, Continuous Liquid Interface Production (CLIP) is an SLA similar technique which achieves speeds up to 100 cm/h by creating a dead zone i.e., oxygen-containing zone, that ensures photo-polymerization (Alhnan et al., 2016a).

Direct Energy Deposition (DED) and Sheet lamination

Direct Energy Deposition is an additive manufacturing process in which focused thermal energy such as laser, electron beam, or plasma arc, is used to fuse materials by melting as they are being deposited (ISO/ASTM Internarional, 2013). Material is fed in either wire or powder forms for the heat source to melt as it leaves its nozzle, forming complex shapes. This technology can be used to build up a print layer by layer, but it can also be used to repair objects. For this reason, DED is often used more for repair than to create entirely new printed items (Nikhil, 2021).

Sheet lamination is a form of 3D printing that functions by stacking and laminating sheets of very thin material together in order to produce a 3D object. The sheets are initially cut by a laser or knife and then the material layers are fused together using a variety of methods such as applying adhesion or by laser

depending on the raw material. Common materials used in sheet lamination are paper, polymers, and metals. This technology is the least accurate 3D printing technology and is used to produce cost-effective, non-functional prototypes at a relatively high speed (Nikhil, 2020).

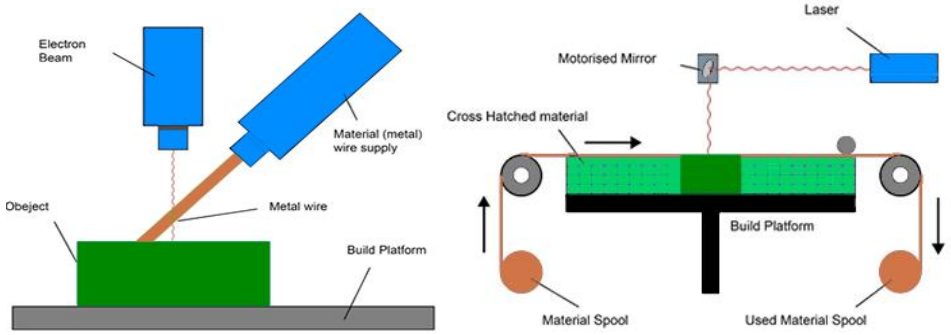


Figure I.1.27: Direct Energy Deposition (left) and Sheet lamination (right) 3D printing technologies (Nikhil, 2021, 2020).

I.1.4. Application of 3D Printing in Pharmaceutics

Since its introduction, 3DP has evolved rapidly and is currently being used along a wide range of industries, such as automotive, architecture, construction and aerospace (Bak, 2003; Berman, 2012; Joshi and Sheikh, 2015; Liu et al., 2016; Perkins and Skitmore, 2015). It is highly flexible, robust, multilateral, cost effective, precise, and fast. These attributes draw the attention of the researchers and industries in the pharmaceutical field opening new possibilities to product development and manufacturing (Attaran, 2017). 3DP allows the production of personalized dosage forms meeting the patient's unique needs (Skowyra et al., 2015) challenging the 'one-size fits-all' approach (Lamichhane et al., 2019). Within this context, complex geometries unable to be produced with the traditional techniques (Arafat et al., 2018; Isreb et al., 2019; Sadia et al., 2018), designs requiring dose accuracy for narrow therapeutic index drugs (Vakili et al., 2015), which could also be combined with additional active ingredients with tailored release profiles (Goyanes et al., 2017) or the potential of production at the point of need (Araújo et al., 2019) provide a much better outcome in terms of compliance, safety and effectiveness (Alhnan et al., 2016a).

Among its many advantages, agility, precision, and acceleration in the production of multiple versions of a drug for variant populations in short run batches are the ones challenging the traditional manufacturing technologies. This was realized by the recent FDA approval of Spritam®, the first 3D printed, instantaneously disintegrating formulation (Aprecia Pharmaceuticals, 2015). Aprecia's SPRITAM® dosage form adopts ZipDose® technology in which the delivery system with a high drug dose is disintegrating in seconds with "*a sip of water*" (Aprecia, 2018). This was feasible due to the uniform porous structure facilitated by a 3DP process, which links powder together (Norman et al., 2015), adopting the printing-based inject systems principles. In line with the above, various research groups developed fast disintegrated tablets by constructing complex formulation designs, such as tablets with "*loose powders in their inner regions*" (Yu et al., 2009) or "*oral fast dispersible tablet with drug release within a few seconds*" (Monkhouse et al., 2000; Zheng and Huang, 2016).

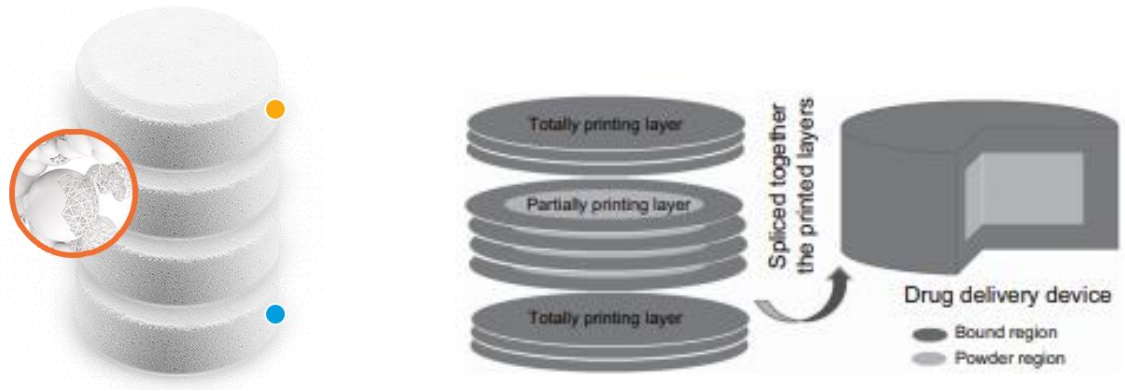


Figure I.1.28 The first FDA approved 3D printed pharmaceutical form (Aprecia, 2018) (left), 3D printed fast disintegrated tablets (Yu et al., 2009) (right).

Apart from fast disintegrating tablets, 3DP has allowed the development of new complex formulation designs such as void tablets that were not able to be constructed with the conventional manufacturing methods. For example, semi-solid extrusion (EXT) was used to form "*bilayer tablets with high drug loading*" and introduced a new and easier way of tablet production (Alhnan et al., 2016a; Khaled et al., 2014). Similarly, core-shell structures containing "*the drug in the inner part and placebo walls*" (Jonathan and Karim, 2016; Wang et al., 2006; Wu et al., 1996) or compartmented structures ware employed by many researchers to create drug-loaded implants with different drug release profiles (Huang et al., 2007; Water et al., 2014; Wu et al., 2014, 2009). Another research team (Okwuosa et al., 2017), fabricated a shell-core delayed release tablet using dual-nozzle FDM 3DP and polymers, in which the inside core includes the API, while the outside shell serves as an enteric coating. This study demonstrated the potential of fabricating patient-specific pH-responsive tablets in one step. An oral dosage form fabricated by 3DP, which encapsulates a toxic or potent API in the core which then coated, providing protection and isolation of the core has also been developed (Payumo et al., 2011).

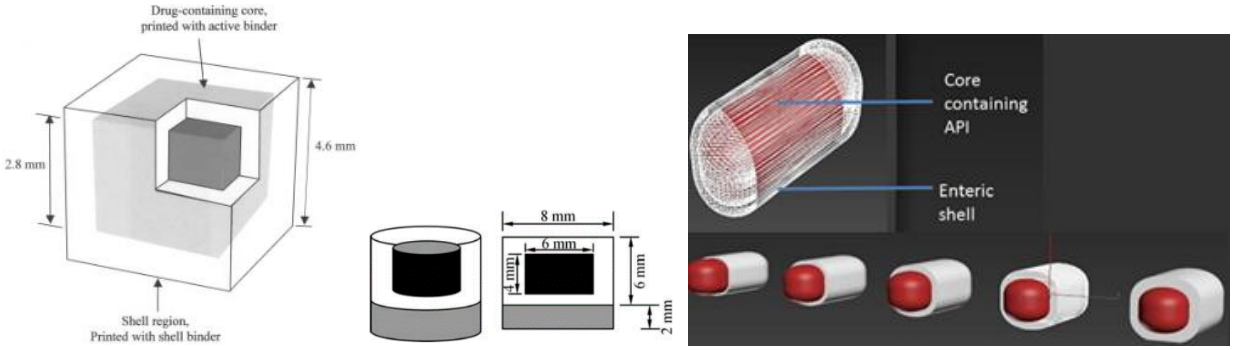


Figure I.1.29: Shell-core constructions (Wang et al., 2006; Wu et al., 2009*; Okwuosa et al., 2017)*

3DP is the ideal technology for producing individualized tailor-made pharmaceutical products. Due to its versatility, changing the shape or size of a drug product according to patient's needs is relatively easy (Alhnan et al., 2016a). This can be done with a simple modification in the CAD software, which is more convenient and cost effective than changing the manufacturing requirements in a traditional set-up. Groups of patients such as pediatric or geriatric are in need of individual dosage units as the treatment demands adaptation especially, when highly potent drugs with narrow therapeutic index are used. Due to its accuracy, 3DP is capable of producing precise and extremely low-dose products that fit to the patient's needs, while

maintaining the content uniformity. This was demonstrated by various researchers like Katakam et al. who printed extremely low-dose products containing as little as 3 ng of API (Katakam et al., 2015), while other researchers showed accurate dosing in children (Norman et al., 2015; Sanderson, 2015). Within the same context, various scientific teams enabled personalized dosing of theophylline and prednisolone (Norman et al., 2015; Sandler et al., 2011; Skowyra et al., 2015; Vakili et al., 2015).

The development of delivery systems with complex or modified drug release profiles is one of the most explored uses of 3DP, facilitated through the fabrication of different shapes and geometries of the dosage form. The tailored combinations of drugs, drug doses, and the desired release kinetic properties that 3DP can offer, has made possible the production of multipurpose therapeutic systems such as orodispersible, sublingual, fast-dissolving drug delivery formulations that rapidly disintegrate in the oral cavity or immediate-release tablets that can be fit in individual needs (Jamróz et al., 2017; Kempin et al., 2018; Musazzi et al., 2018; Solanki et al., 2018). In this respect, many scientists have designed modified-release oral dosage medicines, using 3D printing to achieve a preferred therapeutic goal (Siamidi et al., 2020).

For example, the manufacture of dual compartment dosage units with the combination of two negative interacting antitubercular drugs has been demonstrated by coupling FDM 3D printing with hot-melt extrusion and creating tailored-dosage oral drug delivery units with modified-release properties (Genina et al., 2017). In the same manner, custom-built filaments via hot-melt extrusion have been created and with these by applying FDM 3D printing created oral solid dosage forms with zero-order release kinetics (Gioumouxouzis et al., 2017). Another research team manufactured tablets with varying shapes such as cube, pyramid, cylinder, sphere, and torus containing acetaminophen and realized that the drug's release dependents on the surface-area-to-volume ratio and not on the tablet surface area, indicating the effect of the shape on the release profile (Goyanes et al., 2015c). Tablets of various shapes may alter the drug dissolution profiles and can aid in the design of new dosage forms with specific pharmacokinetic characteristic targeted to different sites in the gastrointestinal track (Siamidi et al., 2020). Within the same context, the fabrication of solid dosage forms with complex geometries such as honeycomb based, using hot-melt 3D inkjet printing, which showed controlled release has also been demonstrated (Kyobula et al., 2017). This study also verified that 3D printing can be utilized as an alternative production approach to achieve the construction of different geometries and subsequently various release profiles for personalized drug products (Siamidi et al., 2020). In 2015 a research group combined three different technologies for the fabrication of controlled-release capsule-shaped tablets with enteric coating. Hot-Melt Extrusion (HME) was used for the filament creation, FDM 3DP for the fabrication of tablets, while for the coating, a bottom spray fluidized bed coater was employed. These tablets had an initiation in release at the small intestine and continued in a sustained manner throughout the large intestine and colon (Goyanes et al., 2015b). The same group proved that the proper selection of the printing parameters can modify the release profiles of amino salicylic acid tablets (Goyanes et al., 2015a). Moreover, distinctive modified-release profiles depending on drug solubility and drug loading was proved by performing dissolution tests on caplets produced by FDM (Goyanes et al., 2016).

Additionally, a research team managed to formulate modified-release tablets with stereolithographic 3D printing (Wang et al., 2016), while powder bed/jetting 3D printing has been employed to construct a matrix tablet with modified release of acetaminophen, which released via a two-dimensional surface erosion mechanism and almost all of the drug could be released linearly in 12 h (Yu et al., 2007). A group by Zhang et al. managed to 3D print tablets showing more extended drug release rates than the directly compressed tablets by producing solid-dispersion filaments with hot-melt extrusion (Zhang et al., 2017). Using the same

extrusion methods, Pietrzak et al. fabricated tablet systems which combined immediate and extended-release (Pietrzak et al., 2015). Extended release tablets were also produced by another research group (Skowyra et al., 2015) using FDM 3D printing, indicating the feasibility of FDM to control the dose of extended-release tablets. Researchers have also demonstrated the use FDM 3D printing to fabricate novel personalized oral drug delivery systems produced at the point of use (Goyanes et al., 2015d). This novel drug delivery systems consisted of either of multiple layers of different active ingredients or a two-compartment device, comprising of a caplet in caplet (DuoCaplet), with each compartment containing a different drug. When a combination of two active ingredients was used, the multilayer system showed similar release rates for the two drugs but faster rate when the drug loading increased. In DuoCaplets, the active ingredient in the external caplet released first and depending on the caplet's characteristics, the ingredient in the core caplet released later with a lag time. In another study, the same group showed the possibility of employing FDM 3D printing for the production of delayed-release solid dosage forms, without the need of enteric coating (Goyanes et al., 2017).

Two-compartment capsular devices with pulsatile drug release have also been manufactured. The capsular device contained incompatible drugs or differing drug formulations and through the assembly of the compartments with different wall thickness and/or composition, the release was varied (Maroni et al., 2017). Finally, the research team by Rowe et al. constructed pulsed release tablets containing combinations of active ingredients showing immediate or extended release depending on the environmental pH (C. Rowe et al., 2000).

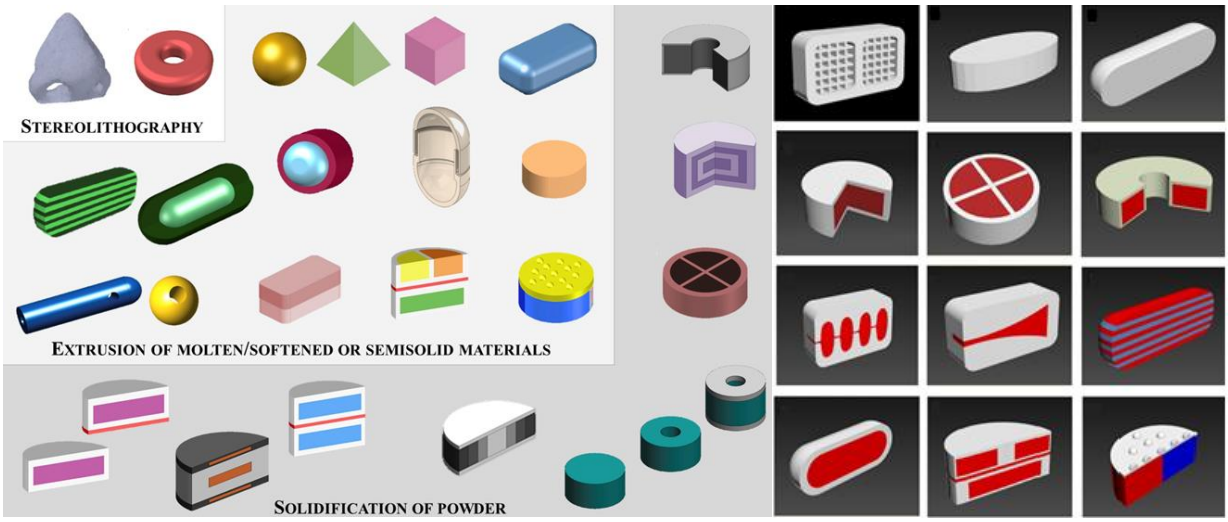


Figure I.1.30: Examples of different shapes and geometries of 3D printed dosage forms (Alhnan et al., 2016a; Zema et al., 2017)

Within the frame of the "polypill" concept, 3DP could facilitate its realization by combining all patient's medications into a single dosage form. The construction of *"multi-active tablets and multi-compartment polypill*" delivering different drugs with customized release mechanisms has been demonstrated by various researchers (Alhnan et al., 2016b; Khaled et al., 2015a, 2014). More specifically, bilayer tablets with an immediate-release and a sustained-release layer were produced with FDM 3D printing. Also, a novel complex geometry "five-in-one" polypill was created, where the different drugs were separated to avoid incompatibilities, while immediate and sustained drug release mechanisms were demonstrated. The same group (Khaled et al., 2015b) also has fabricated "polypills" with well-defined and separate controlled release profiles for three different drugs, namely, captopril, nifedipine, and glipizide. The captopril

compartment exhibited zero-order drug release from an osmotic pump, while the others showed either first-order release or Korsmeyer- Peppas release kinetics dependent on the active/excipient ratio used (Siamidi et al., 2020).

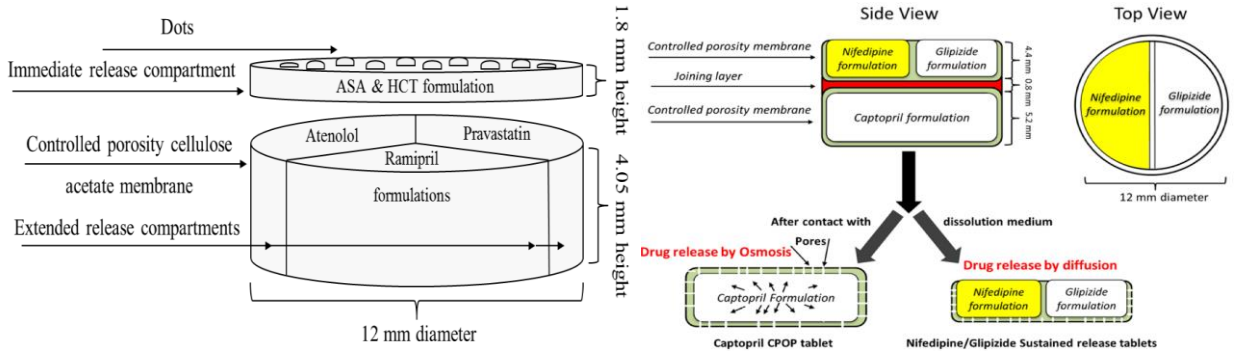


Figure I.1.31: The "polypill" concept (Khaled et al., 2015a, 2015b).

Last but not least, 3DP can be used as an on-demand manufacturing technology at the point of need, as the final products could be made within minutes. Therefore, it could be used in emergency and operating rooms, ambulances or crisis zones for printing on time at the point of use, while product development could also be accelerated (Norman et al., 2015). Finally, the research group by Khaled et al. showed that 3DP might be a tool for producing drug products with short-stability profile for immediate consumption at the point of need (Khaled et al., 2014) .

Many reviews have been published emphasizing on the aforementioned applications of 3DP (Drăgănescu et al., 2019; Giannatsis and Dedoussis, 2009; Gioumouxouzis et al., 2019; Goyanes et al., 2015d, 2015c; Jonathan and Karim, 2016; Khaled et al., 2015a; Lamichhane et al., 2019; Norman et al., 2015; Pereira et al., 2019). However, the literature on the use of 3DP specifically for the coating or partial coating of solid dosage forms is limited while the materials used consist of a specific range of polymers (Konta et al., 2017).

For example, two research teams (Katstra et al., 2000; Yu et al., 2007) fabricated controlled release tablets with a powder-bed 3D printer and polymeric materials. The printed tablets consisted of placebo coating layers on top and bottom of the tablets, while the core contained the API and the polymer, leaving the lateral surface uncoated. The API's release was controlled by the polymer content in the core of the tablet. Another research team (Melocchi et al., 2016), demonstrated the potential of creating filaments from different solubility grade polymers. These filaments can be employed by FDM 3DP and construct immediate or modified release coating layers at tablets or whole capsules. Partial coating by 3DP was also applied in drug loaded implants for modifying the release profile of the API. Cylindrical implants of API and polymer matrix material with 3D inkjet-printing have also been constructed (Huang et al., 2007). The API was either encapsulated in the core of the implant surrounded by the polymeric matrix without any free sides or in the same manner encapsulated with an additional bottom region of API.

The literature review indicated a range of materials used, mainly consisting of polymers, including Polyvinylpyrrolidone (PVP), Hydroxypropyl Methylcellulose (HPMC), Eudragit®, Polyvinyl Alcohol (PVA), Polyethylene Oxide (PEO), Polycaprolactone (PCL) and Polylactic Acid (PLA). On the contrary, a very limited number of studies reported the manufacture of lipid-based drug delivery systems with 3DP (Vithani et al., 2019a). A research group (Vithani et al., 2019a, 2019b) for example, used 3DP technology for the preparation of solid self-micro emulsifying drug delivery systems. A different research team

(Kyobula et al., 2017) used beeswax as a carrier to produce drug-loaded solid dosage forms. Finally, a research team (Içten et al., 2017) developed a dropwise 3DP technique for preparing amorphous self-emulsifying drug delivery systems based on lipids. Nevertheless, no publications were found demonstrating the use of glycerides for the coating of tablets with 3DP (Tsintavi et al., 2020).

While, this section summarized the major 3DP capabilities and their potential benefits, 4D Printing is emerging (Khoo et al., 2015).

I.1.5. Strengths and Weaknesses

Three-dimensional printing (3DP) is a relatively new technique especially in the pharmaceutical field. As presented in previous sections, there are many types of 3DP technologies that have been applied in the pharmaceutical research with many manufacturing advantages over the conventional manufacturing techniques and can offer many opportunities in dealing with some difficulties in pharmaceutics (Yu et al., 2008). 3DP is an additive manufacturing technique that can provide alternative ways of novel product development. Nevertheless, there are some limitations that should be overcome before 3D printed drug delivery systems can be commercially available.

I.1.5.1 Strengths and Opportunities

Novel drug delivery systems

In conventional tablet manufacturing challenges in formulation, scale-up or commercial production have limited the applicability of novel drug delivery systems. Thus, new technologies such as 3DP are the ones challenging these limitations and can overcome such problems. Compared to conventional technologies such as compressing, 3DP has many advantages which result in research and development of alternative, novel dosage forms. Among these advantages are flexible and scalable manufacturing processes, fast prototyping, feasibility of commercialization and on demand manufacturing. 3DP products can achieve high performance in the reproducibility, accurate dosage, and accurate control of the desired release profiles (Yu et al., 2008).

Flexibility

One of the main advantages of 3DP is its flexibility in the design of complex dosage forms. In majority, the traditional manufacturing techniques rely on the physical and chemical characteristics of matrix polymers to achieve the desired release. Thus, a lot of research effort has been spent on developing new polymers or modifying the physicochemical properties of the existing ones. Moreover, the designs of drug delivery systems that can be manufactured by conventional techniques are within a specific range and often involve multistep manufacturing, different raw materials, or significantly different types of manufacturing equipment. For example, in order to produce an enteric-soluble tablet, different raw materials and equipment are needed for the preparation of the core tablet, such as a combination of excipients capable of immediate release and a rotary tableting machine. For the next step, the enteric coating, a combination of different excipients that disintegrate only in enteric pH and a coating pan or a fluidized bed are needed. All of these processing steps may be time consuming and demanding to be developed and performed on daily basis. On the contrary, 3DP is a computerized fabrication technique that can rapidly produce highly complex three-dimensional objects. Multiple drugs and materials can be deposited accurately in specific positions, offering the possibility of producing drug delivery systems with unique designs, compositions,

and surface texture, achieving sustained, immediate, controlled release or combinations. 3DP is capable of producing designs with different porosities or combinations of multiple drugs and release modifiers, that are impractical or even impossible with conventional technologies. These capabilities offer the potential of direct manufacturing of dosage forms in one single step, with repeatable and model-based operations. Finally, by simply varying one or more process or system parameters such as layer thickness, line spacing or the composition of the raw materials, the desired drug release profile can be achieved. This is due to the flexibility of 3DP that improves the design and performance of the drug delivery systems and minimize design-related issues that are normally associated with traditional processes.

Accuracy

Another advantage of 3DP is the improved product performance. In 3D printed drug delivery systems, the dosage can be accurate at nanogram levels, the toxic or potent drug can be positioned as desired in the dosage form, the drug can be dispersed accurately, the release profiles are highly reproducible and in terms of manufacturing process, the scale-up is easier and nonproblematic (Norman et al., 2015; Sanderson, 2015; Payumo et al., 2011).

Acceleration of the development phase

Additionally, 3DP can reduce the amount of time needed at the development phase of a product. It allows the production of extremely low batches or individual items to be fabricated within a single manufacturing run. Thus, a rapid and parallel screening of many prototypes is feasible in short time. Thus, the development time of new products is significantly reduced compared to conventional methods. Furthermore, 3DP simplifies the transition from development to manufacturing. Faster and less costly scale-up is possible by simply using either multiple printheads or a faster machine.

Product Customization

The customization of drug delivery is one of the many advantages of 3DP, especially in the oral dosage form production. According to the patient requirements and personal needs, the active ingredient can be included in the dosage form and achieve both personalized dose and release pattern. 3D printing aids also in achieving multidrug combinations with complex release profiles (Sandler and Preis, 2016). The combination of tailor-made products with the on-demand manufacturing is the characteristic that makes 3DP advantageous compared to the conventional production processes (Siamidi et al., 2020).

I.1.5.2 Weaknesses

Clogging

The weaknesses that are associated with 3DP systems and processes are mainly found in print heads and binder formulations, powder deposition, software issues, optimization parameters, and post-treatment methods. The most common problem that is faced with nozzle based 3DP systems is the clogging of the nozzle. Depending on the 3DP technology, clogging can be caused by many different reasons, such as that the binder dries up during inactive periods of time, the powders agglomerate around the nozzle or incorrect melting temperatures are used. Thus, the development of proper binder formulation, powder mixture or filament composition in combination with the proper processing parameters depending on the 3DP system is essential.

Parameter optimization and printing time

In a 3DP process, many parameters should be considered, among them are printing rate, printing passes, velocity of the print head, interval time between two printing layers, distance between the nozzles and the printed layer, and layer thickness. Thus, the optimization of all of these parameters in order to achieve products with high performance requires a lot of research. On top of that, 3D printing has a low production rate, as it requires several hours to complete the printing and post-treatment.

Post-processing

In some cases, 3D printed products require post-processing in order to achieve better product performance. Post-treatment can result in improved surface finish, elimination of void spaces or improved consistency. Thus, the post-treatment method selected needs to be properly designed to achieve the desired outcome (Yu et al., 2008).

Regulatory framework

Furthermore, the limited regulatory framework supporting both the use of additive manufacturing equipment for the fabrication of pharmaceutical forms and the 3D printed pharmaceutics themselves do not encourage the development of such techniques at an industrial level. Problems such as the reuse of unbound powder supporting the drug delivery system or the environmental considerations of the waste of such materials are yet to be solved.

Individualized limitations

Finally, each 3DP technology has its own limitations. For example, in FDM 3DP technique only thermostable drugs and the few available compatible excipients may be used, while with stereolithography, the challenge lies on the potential drug degradation due to the exposure to UV light that induces polymerization reaction (Prasad and Smyth, 2016; Siamidi et al., 2020).

I.1.5. Industry 4.0

I.1.5.1 Historical Background

In modern history, Industrial Revolution can be defined as '*the process of change from an agrarian and handicraft economy to one dominated by industry and machine manufacturing*' (Trinder, 1997). In essence, novel ways of working and living were introduced to society due to the technological changes and thus transformed society. Technological, socioeconomic, and cultural features such as new basic materials and energy sources, new machines, the division of labor, improvements in transportation and communication, economic and political changes or the needs of new working skills are ones involved and led to the industrial revolution.

First industrial revolution

The first industrial revolution took place mainly in Great Britain in the period of 1760-1830. The power of steam replaced the manual labor. During industry 1.0 manufacturing was based on stationary stem engines, machines that were developed and improved by Thomas Newcomen, John Smeaton, Richard Roberts, and James Watt. The first industry that implemented the use of such technologies and was the dominant industrial sector at that time was the textile industry (Landes, 2003). Furthermore, at this period, the

consumption of iron, as well as chemical raw materials (solvents, chemical reagents, etc.) increased rapidly. Finally, from the 1870s onwards, the production of industrial scale begins, which is based on new tools, such as the screw cutting lathe, cylindrical machines and pulverizing machines, while all factories now have advanced machines that operate with the help of steam power (Britannica The Editors of Encyclopaedia, 2021; Landes, 2003).

Second industrial revolution

The beginning of the second industrial revolution is dated around 1850 and lasted until the late 20th century. The fundamental element of the second industrial revolution was the utilization of electricity in the industries. Thus, the introduction of hydroelectric power into industrial production allowed the rapid industrialization of many companies, which did not have access to coal. By the 1890s, the introduction of electricity to the industries has started and by the 1930 centralized electrical stations had been built, which led to the decrease of cost of energy. During this period, the machines that operated with steam were replaced with electrical machines, which led to the increase of productivity by even 30% (Devine, 1983).

The second industrial revolution also introduced the term of mass production, referring to the industrial production of large quantities of standardized products. Mass production spread during the 1910s and 1920s mainly by Henry Ford, who introduced the electric motor in the then known technique of sequential production. A typical example of mass production is the "*Assembly Lines*", according to which the various parts are added in sequence in order to produce the final product. Thus, the industrial process becomes much faster, while at the same time there is the possibility of producing more products, as employees focus on an individual department, instead of producing a product from beginning to end. This led to low unit cost per processed product.

Even though mass production lowered the cost of products, it did not have the ability to respond to changes in demand and adapt to changes in specific design requirements. Therefore, mass production in this time period is characterized as inflexible because it is difficult to introduce modifications and changes, while all products are almost the same, resulting in not meeting the personal needs of all customers.

The exploitation of many natural and synthetic materials that have not been utilized until that period, such as lighter metals, rare earths, new alloys, and synthetic products such as plastics, as well as new energy sources and mainly the use of steel are some of the characteristics of the new industrial era, which is tightly linked to mass production (Britannica The Editors of Encyclopaedia, 2021). The new materials in combination with developments in machines and tools lead to the gradual evolution of the chemical industries, which use petroleum products, while at the beginning of the 20th century the automobile industry also developed. The increasing availability of petroleum products has drastically reduced the use of coal as a fuel and at the same time expanded the possibilities for the industrialization of many companies.

Third industrial revolution

The third industrial revolution was introduced in the second half of the 20th century by the emergence of nuclear power and is directly related to the rapid development of electronic media. In terms of science, biotechnology started developing and at the same time, efforts were made to promote renewable energy sources, "green energy" and information technology. In industrial production, automation started to appear.

The main features of this period are the adoption of electronic means and automated controls in industrial production (transistors and later PCs, robots, software, etc.). Until the end of the 3rd industrial revolution, there was an effort to shift from mass production to mass adaptation, meaning that apart from the adaptation

of electronics and automation, the goal of industries was to meet the individual needs of the end users within what today is called "*smart*" software. The integration of innovative technologies and materials with improved properties with the ability to adapt to changes in the environment, such as advanced robotic systems, became the goals of this era. Additionally, 3DP is beginning to appear in the industrial production environment. Given the ease of digital design, there is the possibility of direct production of prototypes and products through 3DP.

Fourth industrial revolution – Industry 4.0

Previous industrial revolutions liberated man from the power of animals, using the power of water and steam to mechanize production, and made mass production possible through the use of electricity. The third industrial revolution led to the widespread use of electronic technology and information technology in order to automate production (Schwab, 2018). A few years after the second millennium, a new industrial period gradually began, the fourth industrial revolution. This industrial revolution is fundamentally different as for the first time an industrial revolution is based on a new technological phenomenon, digitization, and not on the emergence of a new form of energy. It is characterized by a number of new technologies, which affect not only the operation of industries, but also the economic policy of each state, as well as promotes new ideas and a new approach to what it means to be human (Schwab, 2018). Through digitization and networks, billions of industries and people can be connected, allowing the creation of a virtual environment, which aims at the interaction of all means of production, thus enabling more correct decisions in real time (Ahuett-Garza and Kurfess, 2018).

The fourth industrial revolution brings digital, physical, and biological systems in direct contact, while at the same time aiming at the integration of innovative technologies, in order to continuously improve the efficiency of the production system and aims at the autonomous operation of machines without human intervention. This is the main difference with the third industrial revolution. In other words, the equipment of the third industrial revolution is being upgraded to have the ability to interact by exchanging data in real time through the technology of the Internet of Things (Schwab, 2016).

The image below illustrates the four industrial revolutions, as well as the basic characteristics of each.

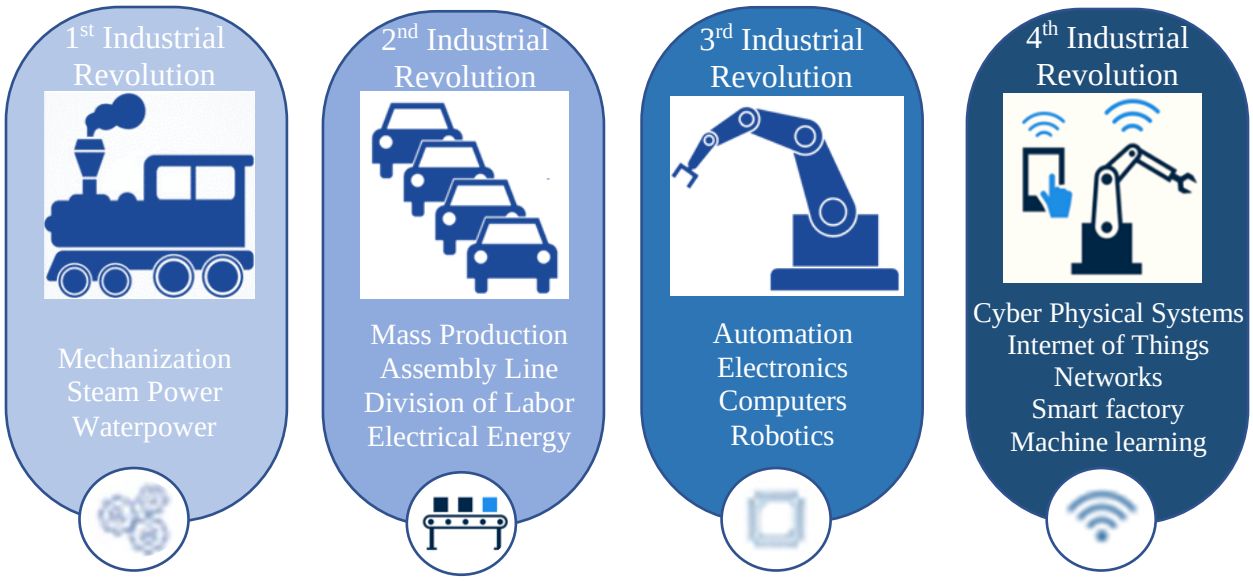


Figure I.1.32: The four industrial revolutions

I.1.5.2 The pillars of Industry 4.0

Industry 4.0 is the next step in the digital transformation of the manufacturing industry containing the use of the latest digital technologies in the manufacturing sector. In essence, industry 4.0 describes a system that evolved from a computer controlled automated facility (Industry 3.0), into a system that gathers and analyzes data from the various manufacturing processes and machines to make intelligent decisions in an automated manner (Ahuett-Garza and Kurfess, 2018). "Smart manufacturing", the deployment of Industry 4.0 for the case of manufacturing, represents the adoption of the following constituents:

- Big data:

The definition of big data is "*data that contains greater variety, arriving in increasing volumes and with more velocity"* (Santos et al., 2018). This is also known as the three Vs or more extended the five Vs by adding the terms Value and Veracity. Essentially, big data is larger, more complex data sets, especially from new data sources. These data sets are so vast that traditional data processing software cannot manage them, but these massive volumes of data can offer valuable information resulting in the solution of complex problems that could not be addressed before.

The application of new sensor technologies at various processing steps and equipment generates tons of data that need to be processed. The increasing capacity of the information systems to store and analyze vast amounts of data in combination with the ease of accessibility to these data, are key elements of Industry 4.0. The analysis of trends and behaviors that these data represent, are revolutionizing the manner in which decisions are made (Ahuett-Garza and Kurfess, 2018).

In addition to the vast treasury of data from production and operation systems, customer data is also being fed in to achieve real-time decision making in the manufacturing process.

- Advanced Analytics

Advanced analytics goes hand in hand with big data and has been defined as "*an autonomous or semi-autonomous examination of data or content using sophisticated techniques and tools, typically beyond those of traditional business intelligence, to discover deeper insights, make predictions, or generate recommendations"*. Techniques that are included in advance analytics are data/text mining, machine learning, pattern matching, forecasting, visualization, semantic analysis, sentiment analysis, network and cluster analysis, multivariate statistics, graph analysis, simulation, complex event processing, neural networks (Gartner Glossary, 2022).

- Artificial Intelligence

John McCarthy, one of the founders of the discipline of artificial intelligence, defines artificial intelligence as *"the science and engineering of making intelligent machines, especially intelligent computer programs. It is related to the similar task of using computers to understand human intelligence, but AI does not have to confine itself to methods that are biologically observable"* (IBM Cloud Learn Hub, 2020a). In simpler words, artificial intelligence is a field, which combines computer science and robust datasets, to enable problem-solving based on fully documented scientific data (data driven decisions - science based approach). It includes sub-fields or tools such as machine learning and deep learning, which use artificial intelligence algorithms in order to create systems which make predictions or classifications based on input data. Artificial intelligence programming focuses on three objectives: learning, reasoning, and self-correction. Examples of artificial intelligence are machine learning, machine vision, automation, Natural language

processing, robotics, speech recognition, customer service or recommendation engines (IBM Cloud Learn Hub, 2020a).

- Machine Learning– Neural Networks – Deep Learning – Transfer Learning – GoogLeNet

Machine learning is a key technology for the development of smart manufacturing as through computer techniques useful knowledge can be extracted from the recorded data in an industrial process and the machines can make appropriate decisions based on big data obtained from a factory at any given time. In other words, machine learning gives the capability of pattern detection and classification, detection of faults and failures after occurrence, prediction of future working conditions and replication of actions (Ahuett-Garza and Kurfess, 2018). Ultimately, machine learning means using data to train computers to perform tasks that they would not be able to do through conventional algorithms.

Artificial neural networks, usually simply called neural networks, are computing systems inspired by the biological neural networks of the brain and mimic the way the brain works in order to recognize patterns between vast amounts of data and solve common problems in the fields of Artificial Intelligence, Machine Learning and Deep Learning. Neural networks are a subset of Machine Learning and are the heart of Deep Learning (Chen, 2021; IBM Cloud Education, 2020).

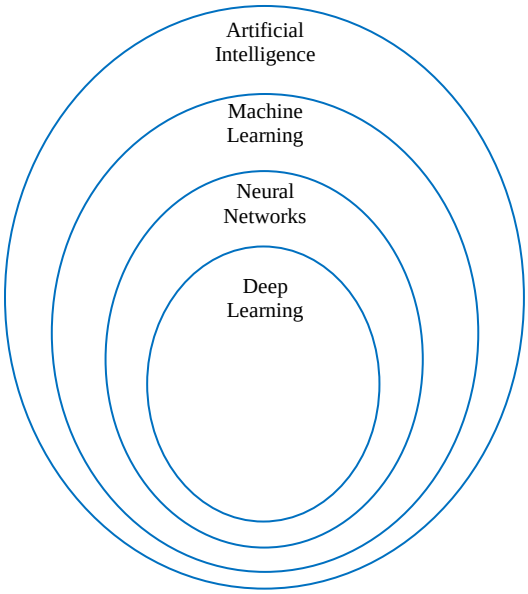


Figure I.1.33: Artificial Intelligence, Machine Learning, Neural Networks and Deep Learning (IBM Cloud Education, 2020; IBM Cloud Learn Hub, 2020b).

Artificial neural networks consist of connected units or node layers, called artificial neurons, which in the most typical architecture are arranged in layers. Like the human brain, each node is connected to another and can transmit a signal to another if the output of any individual node is above a specified threshold value. Neurons and connections typically have a weight that adjusts as learning proceeds. The weight increases or decreases the strength of the signal at a connection, meaning that they help to determine the importance of each transferred input. Typically, neurons are aggregated into layers. Different layers may perform different transformations on their inputs. Signals travel from the first layer (the input layer) to the last layer (the output layer), possibly after crossing the layers multiple times. In essence, a neuron performs a mathematical transformation of the input signal/information according to an activation function that is

appropriately selected for the intended application (typically regression or classification) (Chen, 2021; IBM Cloud Education, 2020).

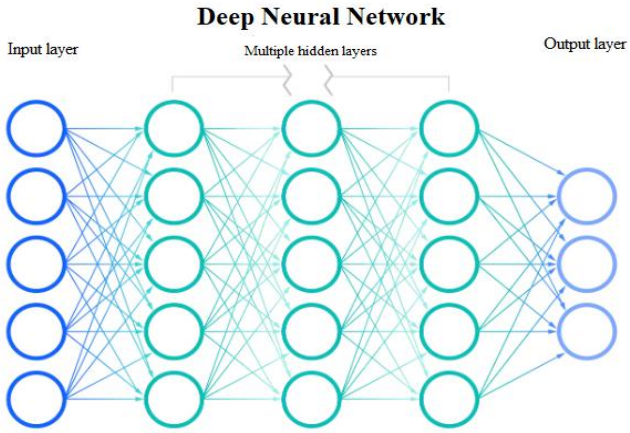


Figure I.1.34: Neural networks (IBM Cloud Education, 2020)

Neural networks rely on training data to learn and improve their accuracy over time. They are trained by processing examples, which contain an "input" and an "output" which are known, and they form probability-weighted associations between the two, which are stored within the data structure of the net itself. By determining the error between the "output" and the "input-target" value in the example, the network trains itself and adjusts its weighted connections according to a learning rule and using this error value. By limiting this error by performing repetitive adjustments, the output of the neural network will be increasingly similar to the target output and thus the training can be terminated based upon certain criteria. This is known as supervised learning. Such systems "learn" to perform tasks by considering examples, e.g., in image recognition, neural networks are trained to identify images with cats by analyzing example images that have been labelled as "cat" or "no cat" by the user, thus identifying characteristics from the examples that they process. Once these networks are fine-tuned, they are powerful in classifying and cluster data at a high velocity (Chen, 2021; IBM Cloud Education, 2020). Other types of training are unsupervised learning and reinforcement learning.

Some basic types of neural networks are:

Perceptron: It is the oldest and simplest neural network consisting of only a single neuron.

Multi-layer perceptron or Feedforward neural network: In this type, each entry point is connected to complex neural nets, where input data travels through various layers of artificial neurons. Every single node is connected to all neurons in the next layer which makes it a fully connected neural network. Input and output layers are present having multiple hidden layers i.e., at least three or more layers in total and it has a bi-directional propagation. This neuron network is applied to speech recognition, machine translation and complex classification.

Convolutional neural network: It is similar to feedforward network but is used for analyzing and identifying visual data such as digital images and photographs. Thus, they are utilized for image recognition and processing, pattern recognition and computer vision. Each neuron in the convolutional layer only processes the information from a small part of the visual field. The network understands the images in parts and can compute these operations multiple times to complete the full image processing.

Recurrent neural network: It is used for analyzing time series data, event history or temporal ordering in order to make predictions about future outcomes. Designed to save the output of a layer, Recurrent Neural Network is fed back to the input to help in predicting the outcome of the layer. The first layer is typically a feed forward neural network followed by recurrent neural network layer where some information it had in the previous time-step is remembered by a memory function. Their main characteristic is that there are connections between neurons that are in the same layer or even between all neurons in all layers (fully-connected recurrent network). Thus, they are utilized in stock market predictions or sales forecasting, imager tagging, auto suggest and grammar checks.

Long Short-Term Memory Networks: They are a type of Recurrent Neural Network that uses special units in addition to standard units. These special units include a 'memory cell' that can maintain information in memory for long periods of time. A set of gates is used to control when information enters the memory when it's output, and when it's forgotten. This architecture lets them learn longer-term dependencies.

Deep learning is a subset of neural networks and machine learning, which is in turn a subset of artificial intelligence. As explained, Machine learning employs algorithms to analyze data, learn from it and use this data to make informed decisions, similar to human thinking, enabling automated tasks. On the other hand, deep learning has additional abilities, as it is able to automatically learn representations from data, such as images, video, or text, without introducing hand-coded rules or human domain knowledge. Thus, deep learning eliminates some of data pre-processing that is typically involved with machine learning (Arm, 2022; IBM Cloud Learn Hub, 2020b). Deep learning neural networks potentially combine many layers, typically with many more neurons than traditional multi-layer perceptron, which can be, among other things, convolutional, fully connected, recurrent etc.

Transfer learning is the method of starting with a pre-trained model and training it for a new related problem domain. The pre-trained network serves as transferred knowledge to be applied in another domain (Jones, 2019). It is an important part of deep learning applications as a smaller amount of time and energy are required to train neural networks as an already trained deep neural network that normally is huge and requires significant resources, is utilized for the solving of a related problem,

In 2014, a team of scientists introduced GoogLeNet (Appendix, Figure A.1), which is a deep learning convolutional neural network architecture designed for image classification and recognition (Szegedy et al., 2014) and consists of 22 layers depth. This network has already been trained to classify images into 1000 objects categories (e.g., keyboard, pencil, animals) or 365 place categories (e.g., field, park, lobby) by a wide range of images with a 224x224 size. The network was designed with computational efficiency and practicality in mind, so that inference can be run on individual devices including even those with limited computational resources, especially with low-memory footprint (Szegedy et al., 2014). This open access neural network can be used and retrained to perform a new task using transfer learning (Mathworks, 2022).

- Internet of Things (IoT) or Industrial Internet of Things (IIoT)

The internet of things (IoT) is one of the main technologies in Industry 4.0 allowing the exchange of big data in real time not only inside an organization but also with the outside world. IoT in conjunction with mobile electronic devices provides instant access to data in order to be processed or transferred at any time from any location via Cloud Computing (Ahuett-Garza and Kurfess, 2018). ENISA defines IoT as "*a cyber-physical ecosystem of interconnected sensors and actuators, which enable intelligent decision making*" (ENISA- European Union Agency for Cybersecurity, 2022). By means of low-cost computing, the cloud, big data, analytics, and mobile technologies, physical things can share and collect data with minimal human

intervention. In this hyperconnected world, digital systems can record, monitor, and adjust each interaction between connected things. Industrial IoT (IIoT) refers to the application of IoT technology in industrial settings.

The IoT converges industries and business areas, uniting Information Technology (IT) and Operational Technology (OT) and contributing to industrial transformation. The main areas of IoT investments include manufacturing operations, transportation, smart grid technologies, smart buildings and, increasingly, consumer Internet of Things, smart home automation and retail.

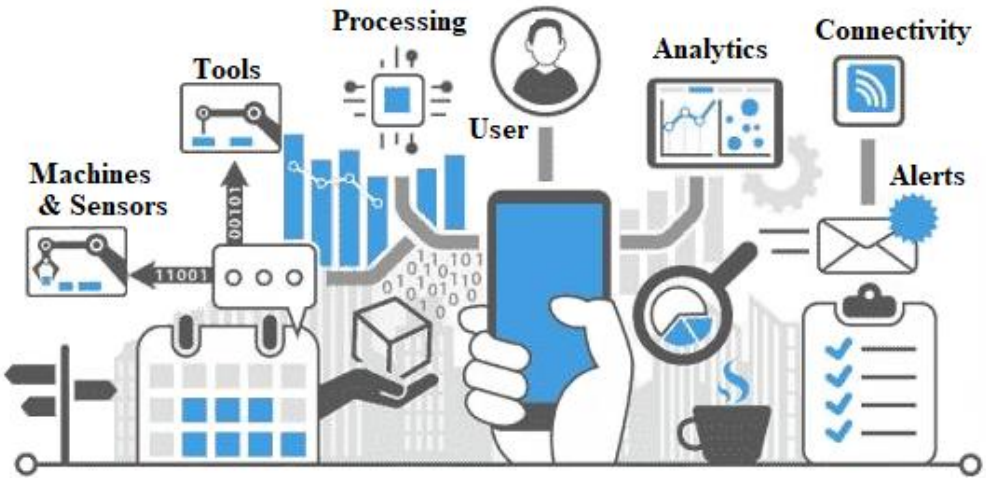


Figure I.1.35: Internet of Things (Open PR, 2022).

- Cyber-Physical Systems (CPS)

Cyber-physical Systems are combinations of statistics, computer modeling, and real time data extracted out of intelligent physical components, objects and systems which get connected through networks, to model the response of a system under multiple scenarios to make decisions in real time. The ultimate goal is to improve the efficiency, at all levels of an industrial system (Ahuett-Garza and Kurfess, 2018). Simply, CPS refer to the bridging of digital (cyber) and physical in an industrial context. They are the enablers of the smart factory concept of Industry 4.0 in an Internet of Things, Data and Services scope, with a focus on processes (i-SCOOP, 2022).

- Digital Twins

Digital Twins are examples of CPS, which is a virtual model designed to accurately reflect a physical object. The object being studied is equipped with various sensors which produce data about different aspects of the physical object's performance. These data are then fed to a processing system and applied to the digital/virtual copy, which can be used to run simulations, study performance issues, and generate possible improvements. These data can then be fed back to the original physical object. Thus, digital twins can model, monitor, and predict the performance of a machine and as a result improve the accuracy and capabilities of a machine or a process in general. In principle, complete factories can have their digital twin (Ahuett-Garza and Kurfess, 2018; i-SCOOP, 2022).

- Augmented and Virtual reality (AR & VR)

Augmented reality and Virtual reality are also examples of CPS. In more detail, through augmented reality, the user can visualize step-by-step procedures of the task to be performed or even get visual instructions in

real time from experts with remote assistance systems. Applications of AR include areas such as maintenance, assembly processes or quality control and are aimed at supporting technicians in their real working environment. Virtual reality has a different orientation than AR, as by VR, exact simulations of products, processes or production plants can be built in order for the technicians to see their operation in first person. Therefore, VR is used for the design phase of products or processes and validation of prototypes, as engineers can check the progress made in a more visual and interactive way through a virtual simulation. In this way, in an early phase, errors can be reduced, and productivity can be increased. Currently, the area where VR is most used in the context of Industry 4.0 is in the training of professionals, as VR enables training in complex or dangerous tasks beforehand and it optimizes the learning process by providing personalized and autonomous training. In short, these technologies combine cyber and physical, allowing operators to obtain critical knowledge easily and visually, enabling the performance of tasks more efficiently (i-SCOOP, 2022; IBM Cloud Learn Hub, 2020a).

- Industrial Robotics

Industrial Robotics deals with the design, production, and operation of robotic systems, as well as their direct application in the control of production processes, in feedback from sensory systems and in data processing. The industrial production of the future will be based on human-robot collaboration, as it will combine the flexibility of human thinking with the precision and high efficiency of robots. As the realization of industry 4.0 is more and more implemented, the use of collaborative robots (cobots), which are robots especially designed to work alongside with people and are used for repetitive tasks, is expected to grow rapidly in the next years. Cobots, in contrast to traditional industrial robots, are equipped with smart sensors and systems linked to the IoT, making them people, location, movement and context-aware, thus safely assist a human. On the other hand, a traditional industrial robot is not designed to collaborate with people. It's designed to complete a very specific pre-defined task without a need for collaboration within a physical workspace (i-SCOOP, 2022).

- Additive manufacturing (AM)

Additive manufacturing is a key technology of Industry 4.0, which has been disrupting how traditional manufacturing works. It is a method of producing three-dimensional objects with the help of a Computer Aided Design (CAD), by depositing materials in layers. AM has been extensively described in Chapter I.1. Today, AM is well established in specific applications characterized by a high level of customization and low volume production. Industrial giants are now using this not just for rapidly building prototypes but even final production models. Additive manufacturing is used in multiple domains such as healthcare, construction industry, defense, retail, pharma, automotive industry, aerospace, on-demand manufacturing (including human tissue and food), smart manufacturing. It is also the subject of intensive research and development (methods, materials, new techniques, application areas, etc.) (Ahuett-Garza and Kurfess, 2018).

- Wearable technology

Wearable technology is the application of "smart" digital and electrical devices, which can be either implanted or worn. Wearable devices, such as activity trackers, are the practical application of the IoT, as electronic and software systems "communicate" directly with the sensors in order to exchange data, without interfering with the human factor.

- Cyber Security

With all this new connectivity comes new risks. Robust cyber security is critical to protecting vital data and instruments.

Figure I.1.36: Industry 4.0 constitutes (https://www.i-scoop.eu/industry-4-0/#64-industry-40-and-technologies-).

This is a small sampling of the constituents of Industry 4.0 and smart manufacturing and what the future industry is going to look like. Industry 4.0 is essentially the digitization of existing processes, which was something that was not technologically possible before. Just like the original industrial revolution drastically increased productivity, so will this digital one. Today, incentives such as the continuous and rapid development of technology and the need to meet the requirements of end users, have led companies to adopt digitization technology, with the sole purpose of connecting each stage of the process. The "factory of the future" in the pharmaceutical industry will be characterized by two additional new elements, the Electronic Batch Record (EBR) and Paperless Manufacturing.

- Electronic batch record (EBR)

In order for an organization to prove that all steps of a process have been executed according to the standard operating procedures and each batch of the final product meets its quality attributes, a batch record is created and filed, which includes data associated with operators, the manufacturing process, equipment, materials, and supplies, data from laboratory information management systems, enterprise resource planning (ERP), process control systems, and more (Stembridge and Adkins, 2018). Traditionally, the batch record is in hard copy and is kept throughout the self-life of a product plus some additional years, used for deviations investigation and traceability. As the batch record is a product quality-controlled document, much time is spent in order to fill, review and correctly file the documents as well as a lot of office space to maintain the

records. Furthermore, all data are collected after the production process and potential deviations are identified after the fact.

On the other hand, when using an automated electronic batch recording system, various databases from different processing steps during the manufacturing process may be used, allowing the monitoring of all critical parameters and trends of the process in real time. The system can simultaneously check if all values are within acceptable limits and in the event of a deviation, in real time, preventive and corrective actions can be implemented so that the whole batch is not excluded. At the same time, all actions can automatically be recorded for traceability reasons (Fortunel, 2017). The implementation of EBR offers real time visibility, it reduces cycle times and eliminates errors due to manual data entry. The data is provided to the users through electronic devices, thus ensuring that no error will occur or that some stage of the process will be omitted, because a piece of paper was lost. Finally, real-time release of batches is possible due to accurate and much faster controls as well as fast access to data from anywhere at any time (Roberts, 2015)(Roberts, 2015).

- Paperless manufacturing

In the same context with EBR, the element of paperless manufacturing refers to the use of software-based electronic systems to monitor and enforce manufacturing production processes, while capturing all information associated with production records. In order to move towards more flexible and faster processes, an obstacle to be overcome is the use of paper. Thus, industries have begun to take advantage of modern technologies of automation and digitization, in order to make the transition to production processes in which paper will not be used (Niels van Os, 2021). Some of the reasons that paper-based processes in manufacturing facilities should be eliminated are firstly that paper processes waste time, secondly that paper processes are subject to human error, paper may be outdated, wasted paper is bad for the environment, paper is not allowed in some manufacturing facilities and finally digitalization provides the opportunity to explore data that is even ten years old, something that is extremely difficult to do with paper (Niels van Os, 2021).

The benefits that paperless manufacturing provides are first of all the minimization of errors and deviations due to human error, thus data accuracy is increased. Also, detailed data collection and recording of process conditions is possible, resulting in a deeper understanding of processes, which leads to optimization; quick, effective, and real-time access to detailed data which in case of a deviation the root cause analysis and the implementation of corrective and preventive actions can be performed immediately. Furthermore, the risk of cross-contamination is minimized both due to the absence of paper (particles, dust) and due to the optimization of the process and material flow. The traceability is increased, the productivity is increased as time is saved from unnecessary actions that do not add value to the final product and last but not least, faster release of batches is possible (Hughes, 2019; Niels van Os, 2021).

I.1.5.3 Pharma 4.0

Pharma 4.0 is an initiative launched by the International Society for Pharmaceutical Engineering (ISPE), aiming in bringing the pharmaceutical industry in line with the concept of industry 4.0, also called Smart Factory (ISPE, 2020). Pharma 4.0 offers practical guidance and regulatory best practice for the industry, in order to speed up the transformation of existing facilities to Pharma 4.0 standard. In essence, the Pharma 4.0 concept builds on Quality by Design and process analytical technology and its implementation to pharma industry aims in its update by incorporating advanced digital elements and enablers into the current

Pharmaceutical Quality System (ICH Q10). This will enable greater opportunities for process improvements throughout the life cycle of pharmaceutical products. Through Pharma 4.0, there is an opportunity of greater degree of connectivity and transparency, which will provide in-line and in-time control over operations and quality and allow faster decision-making. Instead of waiting to check the product only at the end of the manufacturing process, Pharma 4.0 moves to real-time monitoring, using connected systems to enable a truly agile continuous manufacturing system where processes self-adjust based on the data being collected. Since data is at the heart of this system, upgrading to Pharma 4.0 will demand higher levels of security, owing to the increased vulnerability of interconnected automated systems (ISPE, 2020; Tulip, 2021).

ISPE envisioned a holistic approach of Pharma 4.0 aiming at a product's life cycle across all aspects of the industry, including business priorities as well as IT and manufacturing, together with a paradigm shift in company culture. With Pharma 4.0 the goals of each company will be achieved faster, the overall costs will be reduced and the company itself will become more versatile and competitive. Pharma 4.0 is also aiming at a transformation of the manufacturing workforce towards a model of more human-centric workflow, incorporating best practices in respect to health regulations. Also, ISPE envisioned to eliminate data silos within organizations by improving communications through the tools of Industry 4.0 (ISPE, 2020; Tulip, 2021).

According to ISPE the twelve theses for Pharma 4.0 which are the following (ISPE, 2020):

1. Pharma 4.0 extends/describes the Industry 4.0 Operating Model for medicinal products
2. In difference to common Industry 4.0 approaches, Pharma 4.0 embeds health regulations best practices.
3. Pharma 4.0 breaks silos in organizations by building bridges between industry, regulators and healthcare and all other stakeholders.
4. For the next Generation Medicinal Products, Pharma 4.0 is the enabler and business case.
5. For the established products, Pharma 4.0 offers new business cases
6. Investment calculations for Pharma 4.0 require innovative approaches for business case calculations.
7. Prerequisite for Pharma 4.0 is an established PQS and controlled processes & products.
8. Pharma 4.0 is not an IT Project.
9. The Pharma 4.0 Operating Model incorporates next to IT also the organizational, cultural, processes & resources aspects.
10. The Pharma 4.0 Maturity Model allows aligning the organizations operating model for innovative and established industries, suppliers, and contractors to an appropriate desired state.
11. Pharma 4.0 is not a must, but a competitive advantage. Missing Pharma 4.0 might be a business risk.
12. When moving from blockbusters to niche products and personalized medicines, Pharma 4.0 offers new ways to look at business cases.

In the long run, the basic goal of Pharma 4.0 is the gradual digital maturity of the pharmaceutical industry. This begins with elementary computerization and works its way up towards self-regulating, intelligent automated facilities. The simplest step is the replacement of elementary manual processes with basic automation and digital technology. This will contribute to the decrease of process variability and improvement of consistency in product quality, thus increase process and product performance. By simple automation and digital recording, data integrity will be improved, the reporting will become more

qualitative, repetitive tasks can be performed by computers and complex processes will be simplified. The next step is to integrate IoT in all aspects of the industry and especially manufacturing. This will interconnect the whole organization, resulting in improvements is processes and productivity. A digital production record and improved transparency are possible through IoT, which will generate big data that can be analyzed to offer insights into potential improvements, and to help make data-driven decisions in real time. The whole manufacturing process becomes more flexible and faster with more data available in electronic records, a more holistic production picture is available in real time and at any place and a generally improved performance becomes true in accordance with the Right the First-Time approach. The greater availability of data and big data analytics offers a higher degree of predictability, which can be utilized and perform predictive maintenance or fix problems before they occur. At the final stage of integrated digitalization, the automated systems themselves automatically identify potential problems and initiate the appropriate preventive/corrective actions. Thus, non-compliance issues can be avoided and continuous process verification can be performed (Guilfoyle, 2018; Tulip, 2021).

Figure I.1.37: Pharma 4.0 digitalization (Guilfoyle, 2018).

ISPE has developed a pharma-specific maturity Pharma 4.0 Operating Model which describes key enablers and elements of essential importance in the pharmaceutical operations processes, environment, and culture. The four elements of Pharma 4.0 as described by the pharma-specific maturity model (Figure I.1.38) are Resources, Information systems, Organization and Processes and Culture, while the two enables are Digital Maturity and Data integrity (Heesakkers et al., 2019; ISPE, 2020).

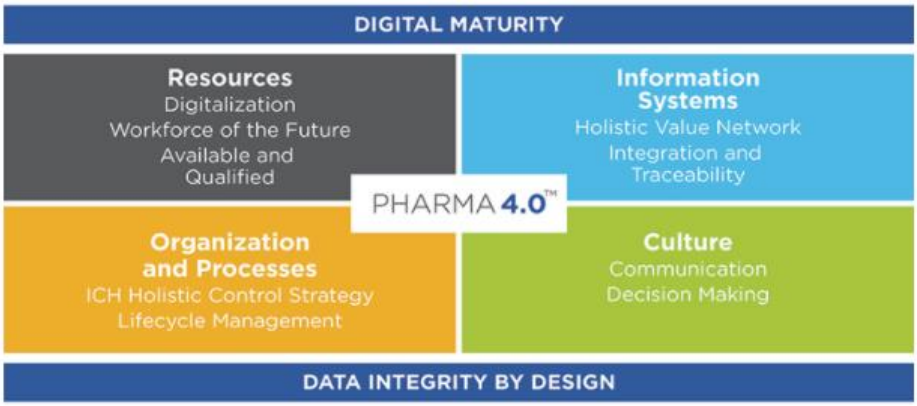


Figure I.1.38: Operating Model of Pharma 4.0 (ISPE, 2020).

The Pharma 4.0 Operating Model was an outcome of a more industry-generic model and its tool Maturity Index, which identifies six maturity levels in order to be able to transfer from digitalization to industry transformation. These maturity levels are the following (Heesakkers et al., 2019):

Level 1 – *Computerization:* This is the initial level of digitalization, and its objective is to simplify repetitive tasks by introducing Information Technology.
Level 2 – *Connectivity:* At this level, the goal is to extend digital connection and integration of business practices.
Level 3 – *Visibility*: The objective is to make databased decisions by real-time digital data.
Level 4 – *Transparency*: At this level, complex interactions between the various process/domains should be identified by running data analytics and interpret the findings to understand effects.
Level 5 – *Predictability:* The system now should be able to predict possible outcomes by simulating future scenarios.
Level 6 – *Adaptability:* Finally, the last step is the system control, meaning be able to adapt itself to new scenarios.

This generic maturity index was expanded for Pharma industry by applying the principles of ICH Q10: Pharmaceutical Quality System (PQS). Table I.1.2 shows the elements and enablers of ICH Q10 and Pharma 4.0, while Figure I.1.39 shows how the six levels of the generic industry maturity model fit the Pharma 4.0 Operating Model. The maturity levels of each element of Pharma 4.0 with examples is analyzed further in the following pages.

Table I.1.2: ICH Q10 and Pharma 4.0 elements and enablers applied to the Maturity Index (Heesakkers et al., 2019).

	ICH Q10 – Pharmaceutical Quality System	Pharma 4.0
Elements	Corrective action and preventive action (CAPA) system Change management Management review	Resources: Digitalization, available and qualified workforce 4.0 Information systems: Holistic value network integration and traceability Organization and processes: Holistic control strategy, life-cycle management Culture: Communication and decision making
Enablers	Knowledge management Quality Risk Management (QRM)	Digital maturity Digital integrity by design

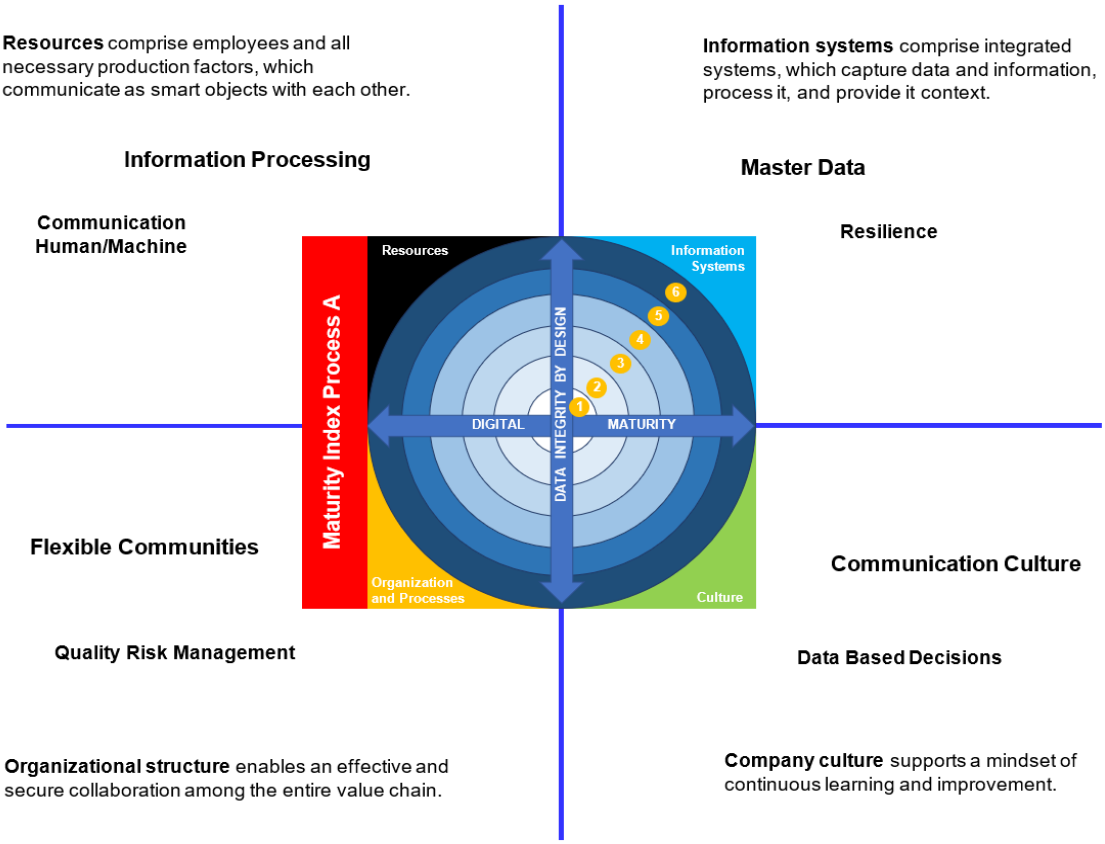


Figure I.1.39: The four elements with exemplary capabilities to be considered in the Pharma 4.0 Maturity Model (Heesakkers et al., 2019)

Resources

One of the elements of Pharma 4.0 is resources, which include any physical asset of the company such as human resources/employees, machinery and equipment, tools, materials, and the final product. One example of resources is information processing. In maturity level 1, databases of information are created by gathering manually information from different computerized systems or paper-based sources. These databases can communicate with each other via sensors and reach at a point where they can provide a digital image of processes and thus have a connected manufacturing process with high visibility. In the next maturity steps, a holistic digital view of the industry and supply chain which are connected is possible, from the active pharmaceutical ingredient via formulation and packaging of the final product to the commercial manufacturing and the patient. Finally, connecting the Quality Risk Management to the digitized system will provide the last maturity level of information processing, as corrective and preventing actions can be enabled and the process can adapt by itself through decision-making processes (Heesakkers et al., 2019).

Another example of resources is the communication between the operator and the machines. The first maturity level requires the physical presence of the operator, while moving to the next maturity level, the operator could adjust the machinery via remote interaction mode. The next step would be to have all the information concerning the operation procedures, events or warning digitalized and available to all employees involved at any time. Additional functions of the machine such as preventive maintenance performed by the machinery is integrated in the next level of maturity, while a fully mature system can lead quality-driven decisions during manufacturing (Heesakkers et al., 2019).

Information Systems

ISPE defines Information systems as "*Sociotechnical systems in which information is provided based on economic criteria determined by people as well as by information and communication technology. Information systems prepare, process, store, and transfer data and information*" (Heesakkers et al., 2019).

Master Data Management is an example of an information system. Initially, the master data are created and maintained in a registry, while new regulatory requirements for data integrity push the organization for creating a data management system where all the information e.g., for the excipients and the API, must be available within the employees of the company. Each substance must have a specific name and a quality-specific reference number. The next level of maturation supports a master data management which can identify and manage all pharmaceutical product-specific data from product development to the end of the life cycle of the product, thus supporting life-cycle management. At the highest mature level, the system could automatically draw life cycle decisions regarding the manufacturing, quality, or supply chain (Heesakkers et al., 2019; ISPE, 2020).

Another example would be the resilience of information systems. The first step is the manual configuration of IT systems, and the assurance that the key systems do not have redundancies. The next step maturity step is when the IT system can isolate failures, while the third level is the implementation of performance statistics and integration of new upgraded servers. Subsequently, the quick identification of failures and the corrective actions provides a further level to maturity and finally, an automated operational reliability risk analyses and reports would be the last step (Heesakkers et al., 2019; ISPE, 2020).

Organization and Processes

The term organization and processes refers to the structure and operational processes of a company both internally and within the industry network. These establish and organize the collaboration within the organization and with other organizations.

Pharma 4.0 promotes flexible communities without silo structures. On the opposite direction lies the structure of a traditional organization, where hierarchy levels and silos make communication difficult. The transition from this set-up to and agile organization can be performed by creating self-organized teams which are directly responsible for their product. Instead of commands, business goals are set, each employ can take part in many teams and is responsible for finding assignments that interest him. The evaluation of each employ's performance is done by the teams he contributes to (Heesakkers et al., 2019; ISPE, 2020).

Quality Risk Management is part of an organization structure and operations. An immature organization there is limited or no risk communication within the different departments of the company and no training for risk management. On the other hand, in a mature organization, risk events are easily and automatically detected and directly communicated in the involved departments through IT systems in order to react in time (Heesakkers et al., 2019; ISPE, 2020).

Culture

The final element of Pharma 4.0 is culture within a company which describes the "soft" aspects of collaboration. Pharma 4.0 promotes a communication culture, which is open and collaborative in contrast to the traditional hierarchy controlled. In terms of data communication, a mature organization needs to move from simply record documentation, approval, and acceptance to a mature communication culture with a knowledge management system with a dispute resolution system. Digitalization can play a key role in

achieving such a transition (Heesakkers et al., 2019; ISPE, 2020). In a highly mature communication culture, the decisions are made based on data with historical data supporting the various choices and not based on the knowledge or intuition of individuals. Automated data analysis, simulations and prediction scenarios can provide the path to decision making and thus through digitalization promote a communication culture (Heesakkers et al., 2019).

The ISPE Pharma 4.0 and its Maturity Index is a roadmap to help pharmaceutical companies to transform into a digitalized organization. For pharmaceutical industries especially, the life-cycle management approach requires the collaboration of different disciplines across the value chain such as development, product transfer units, production, quality control, quality assurance, engineering, supply chain management, marketing, and sales. Furthermore, due to regulatory requirements, data management and availability are critical aspects across the industry. Pharma 4.0 can contribute to this goal.

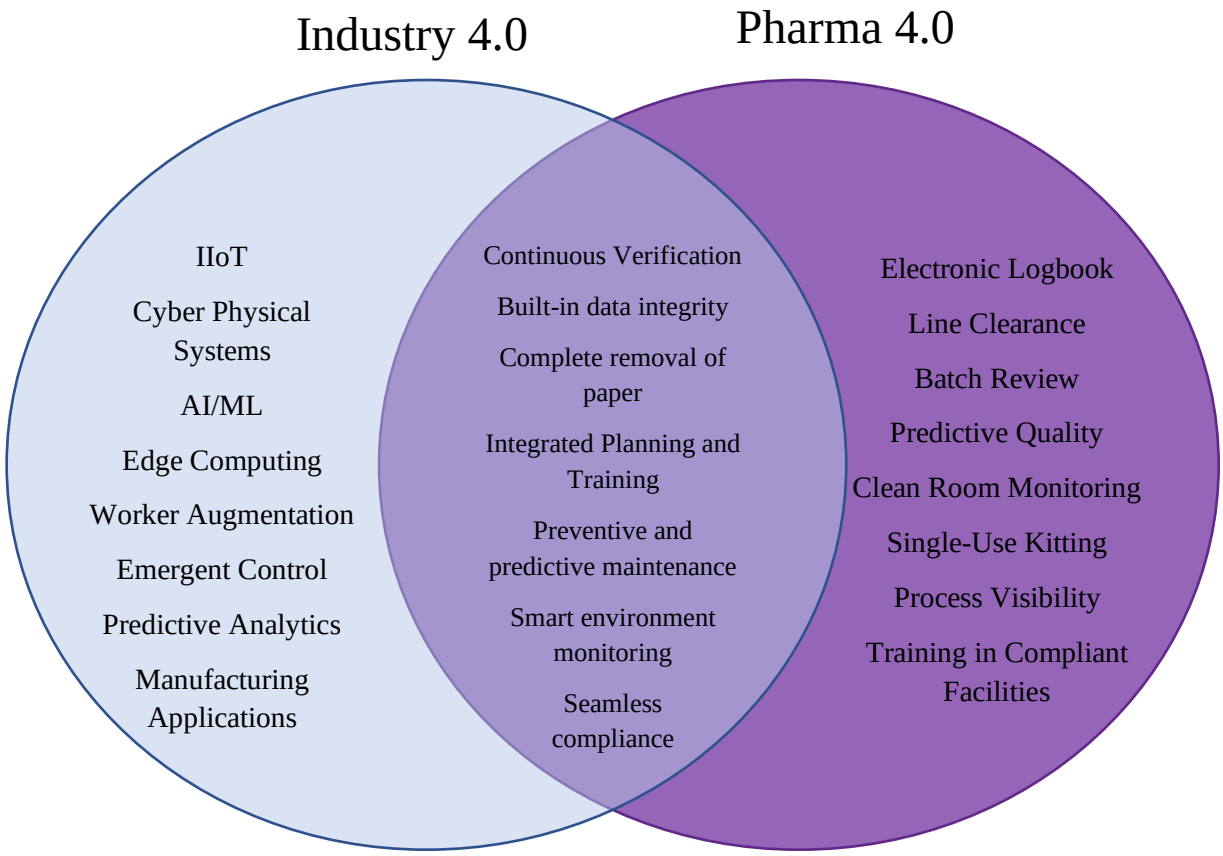


Figure I.1.40: Key similarities and differences of Industry 4.0 and Pharma 4.0 (Tulip, 2021)

Even though the pharmaceutical industry is still a long way from the most advanced, fully autonomous self-correcting automated systems, it is starting to move faster than in previous years. However, in order to adapt these technologies, there is still a lot of lost ground that needs to be covered. Pharma 4.0 is the road map for initiating the necessary steps of the digital transformation, which starts with finding small opportunities for improvement and then scale up towards full integration of digitation. The requirements of Pharma 4.0 demand an agile but flexible approach.

In order to achieve full implementation of these new technologies not only in the manufacturing process but in the whole supply chain, the necessary knowledge, and the continuous training of both the existing and the future workforce is necessary. The mentality and culture of the pharmaceutical organizations needs to change in order to be in line with the principles of Pharma 4.0.

Ongoing collaboration between the adjacent scientific fields of pharmacy, engineering and information and communication technologies is the main driver of change for the required digital transformation to Pharma 4.0 (Rekkas et al., 2021).

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I.2. QUALITY BY DESIGN

I.2.1. Introduction

Quality has been defined in different ways throughout the years. According to American Society of Quality (ASQ, 2002) and European Organization for Quality Control (EOQC Glossary committee, 1989), quality is the totality of all the characteristics of a product or service that constitute its ability to meet the stated and/or the implied needs. Quality is the absence of defects (Georgaki et al., 2010). Other definitions of quality include: quality is inversely proportional to variability or means the fitness for use (Montgomery, 2009). According to other researchers such as Garvin, Pirsing etc., quality is universally perceived but cannot be defined. Whichever the definition of quality, the fact is that the customer defines it according to the fulfillment of his needs and satisfaction.

In the past decade a series guidelines have been conducted in the pharmaceutical field in order to define and establish quality into the final product as well as the manufacturing process. Especially, the guidelines Q8, Q9, Q10 from the International Council for Harmonization focus on the pharmaceutical development and the Quality by Design (QbD) approach, a systematic approach to development that is based on sound science and quality risk management in order to describe an effective pharmaceutical quality system that incorporates all quality regulations and ensures the quality of products throughout the different stages of its lifecycle and thus patient safety.

The basic tool of QbD is Experimental Design or statistical Design of Experiments (DoE). Experimental Design is a structured, organized method for determining the relationship between factors affecting a process and the output of that process (International Council for Harmonisation Q8, 2009). It is a mathematical tool that can enhance the understanding and identification of how process and product parameters affect various response variables such as product quality (Wagner et al., 2014). In other words, as K. Bhote has expressed, design of experiments is the key to the magic kingdom of quality (Bhote, 1991).

Experimental design has been used for decades in many disciplines, including pharmaceutical industry, that aim product quality and process improvement. Through DoE, specific product and/or process variables and their interactions can be identified as statistically important, and their control can optimize the system and product performance. Data generated with the minimum amount of experiments can be analyzed easily and also predict performance under all possible conditions within the limits selected for the experimental design (Wagner et al., 2014). Experimentation is either part of the scientific process or a way through which knowledge about the system and/or the process is obtained. A hypothesis about a process is made, data are generated through experiments about the process and then this information is used to either confirm this hypothesis or form a new one and so on. Experimental design is a major tool in the scientific and engineering field for improving the product realization process and more specifically in new manufacturing process design and development, and process management. The application of experimental design

techniques can offer improved process yields, reduced variability resulting in closer conformance to target requirements, reduced development time and overall costs. Thus, the products are easier to manufacture, they have enhanced performance and reliability, lower cost and are faster available in the market (Montgomery, 2013). A greater understanding of the product and its manufacturing process can result in limitation of variability and thus better control. The manufacturing process and the product can be designed correctly from the beginning i.e. the R&D phase nd quality can be built in by design (International Council for Harmonisation, 2009). This is the essence of Quality by Design.

In the experimental design, purposeful changes are designed and executed in the input process variables in order to observe the change in the quality characteristic(s) under study. The levels of the incoming process variables are changed simultaneously to find the effect of each individual variable as well as their interactions on response (Sethuramiah and Kumar, 2016). DoE is mainly executed in the phase of a product and process development in order to generate all the relevant data, identify the critical product and process parameters that need to be controlled and design or improve the quality of a product and process with the minimum amount of time, expenses, and materials. Overall, experimental design is a tool that offers the design of quality products, the reduction of time during the development phase and the cost of the product as well as the design of robust and reliable processes that can deliver a product of constant quality.

Experimental design, Quality by Design and Quality are directly linked as the first is the tool of providing the knowledge of the product and its manufacturing process and the second is the way of ensuring the design and control of the constant final product quality. Nowadays, all industries in different application fields and researchers use the QbD approach as it provides the design of robust products, the decrease of the time from development to market, the decrease of costs during the life cycle of the product as well as the improvement of their quality and reputation. It is a way of delivering quality products through reliable and robust processes and finally satisfying the needs of the customer.

I.2.2. Basic Definitions

The key definitions related to experimental design are the following:

- Continual Improvement: Recurring activity to increase the ability to fulfil requirements. (ISO 9000:2005) (International Council for Harmonisation Q10, 2008).
- Continuous Process Verification: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated(International Council for Harmonisation Q8, 2009).
- Control Strategy: A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (International Council for Harmonisation Q8, 2009).
- Corrective Action: Action to eliminate the cause of a detected non-conformity or other undesirable situation. NOTE: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005) (International Council for Harmonisation Q10, 2008).

- Critical Process Parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (International Council for Harmonisation Q8, 2009).
- Critical Quality Attribute (CQA): A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (International Council for Harmonisation Q8, 2009).
- Design Space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (International Council for Harmonisation Q8, 2009).

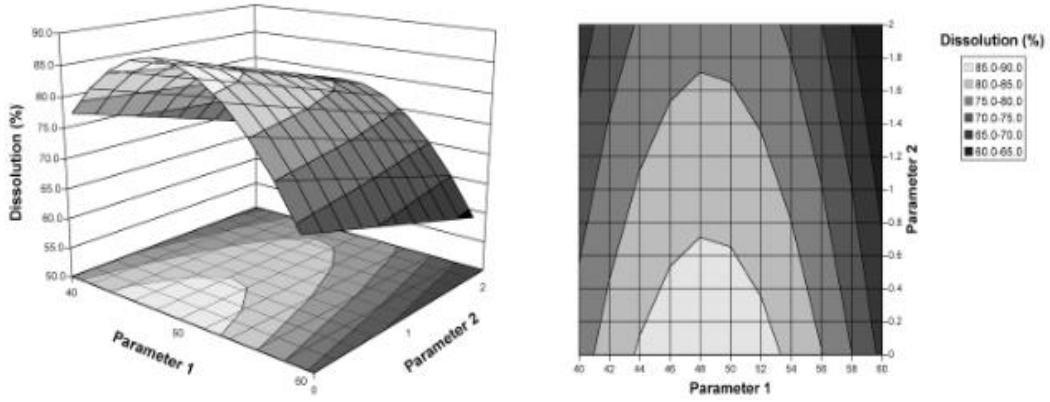


Figure I.2.1: Presentation of Design Space (International Council for Harmonisation Q8, 2009).

- Designed Experiment (Montgomery, 2013; Politis, 2010):
  - A series of tests in which intentional changes are made to the input variables of a process (independent variables or factors) to observe and interpret the change of the output variable (dependent variable or response).
  - An experimental process aimed at finding the cause that connects input and output variables in a process.
  - The research method that allows cause-effect association.
- Detectability: The ability to discover or determine the existence, presence, or fact of a hazard (International Council for Harmonisation Q9, 2005).
- Deviation / Nonconformity: Any non-compliance of an established GMP standard or of approved requirements, specifications, and standard operating procedures. Deviations need to be documented, evaluated and when appropriate, investigated in order to determine the originating causes to prevent recurrence (WHO, 2013).
- Enabler: A tool or process which provides the means to achieve an objective (International Council for Harmonisation Q10, 2008).
- Feedback / Feedforward:
  - Feedback: The modification or control of a process or system by its results or effects. Feedforward: The modification or control of a process using its anticipated results or effects. (Oxford Dictionary of English. Oxford University Press; 2003).

    - Feedback/ feedforward can be applied technically in process control strategies and conceptually in quality management (International Council for Harmonisation Q10, 2008).
- Formal Experimental Design: A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as "Design of Experiments" (International Council for Harmonisation Q8, 2009).
- FMEA: Provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce, or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures (WHO, 2013).
- Frequency or Probability Frequency is the number of occurrences of a repeating event per unit time. It is also referred to as temporal frequency (WHO, 2013).
- Harm: Damage to health, including the damage that can occur from loss of product quality or availability (International Council for Harmonisation Q9, 2005).
- Hazard: The potential source of harm (ISO/IEC Guide 51) (International Council for Harmonisation Q9, 2005).
- Innovation: The introduction of new technologies or methodologies (International Council for Harmonisation Q10, 2008).
- Knowledge Management: Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components (International Council for Harmonisation Q10, 2008).
- Lifecycle: All phases in the life of a product from the initial development through marketing until the product's discontinuation (International Council for Harmonisation Q8, 2009, (International Council for Harmonisation Q9, 2005).
- Performance Indicators: Measurable values used to quantify quality objectives to reflect the performance of an organization, process or system, also known as "performance metrics ", in some regions (International Council for Harmonisation Q10, 2008).
- Pharmaceutical Quality System (PQS): Management system to direct and control a pharmaceutical company with regard to quality (International Council for Harmonisation Q10, 2008 based upon ISO 9000:2005).
- Preventive Action: Action to eliminate the cause of a potential non-conformity or other undesirable potential situation. NOTE: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence (ISO 9000:2005) (International Council for Harmonisation Q10, 2008).
- Product Realization: Achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities (including compliance with marketing authorization) and internal customers' requirements (International Council for Harmonisation Q10, 2008).
- Process: A process is defined as a system of factors or causes that interact appropriately in order to produce a specific result. Essentially, one process converts inputs into outputs under the influence of a number of controlled and uncontrollable factors. These factors participate in different ways in the variability of the outputs of the process (

- Figure I.2.2). Variability is responsible for quality problems (Montgomery, 2009). Each process connects some of the input variables with the output variables through a mathematical model in the form of y = f (x). This is what experimental design aims, to connect mathematically the inputs and outputs of a process by reducing variability as much as possible.

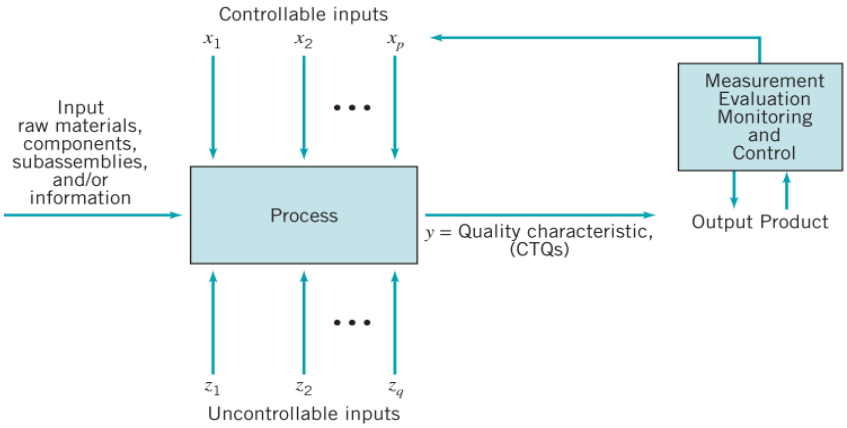


Figure I.2.2: Production process inputs and outputs (Montgomery, 2009).

- Process Analytical Technology (PAT): A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (International Council for Harmonisation Q8, 2009).
- Process Robustness: Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality (International Council for Harmonisation Q8, 2009).
- Proven Acceptable Range: A characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria (International Council for Harmonisation Q8, 2009).
- Process Capability: Ability of a process to realize a product that will fulfil the requirements of that product. The concept of process capability can also be defined in statistical terms. (ISO 9000:2005) (International Council for Harmonisation Q10, 2008).
- Quality:
    - The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as the identity, strength, and purity (ICH Q6A) (International Council for Harmonisation Q8, 2009).
    - Quality is inversely proportional to variability (Montgomery, 2009).
    - Quality means fitness for use (Montgomery, 2009).
    - The totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs (International Standardization Organization, ISO)
    - The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity (from ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances) (International Council for Harmonisation Q8, 2009).

- Quality by Design (QbD): A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (International Council for Harmonisation Q8, 2009).
- Quality Risk Management: A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle (International Council for Harmonisation Q9, 2005).
- Quality System: The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met (International Council for Harmonisation Q9, 2005).
- Quality Target Product Profile (QTPP): A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product (International Council for Harmonisation Q8, 2009).
- Real Time Release Testing: The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls (International Council for Harmonisation Q8, 2009).
- Requirements: The explicit or implicit needs or expectations of the patients or their surrogates (e.g., health care professionals, regulators, and legislators). In this document, "requirements" refers not only to statutory, legislative, or regulatory requirements, but also to such needs and expectations (International Council for Harmonisation Q9, 2005).
- Risk: The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51) (International Council for Harmonisation Q9, 2005).
- Risk Acceptance: The decision to accept risk (ISO Guide 73) (International Council for Harmonisation Q9, 2005).
- Risk Analysis: The estimation of the risk associated with the identified hazards (International Council for Harmonisation Q9, 2005).
- Risk Assessment: A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (International Council for Harmonisation Q9, 2005).
- Risk Communication: The sharing of information about risk and risk management between the decision maker and other stakeholders (International Council for Harmonisation Q9, 2005).
- Risk Control: Actions implementing risk management decisions (ISO Guide 73) (International Council for Harmonisation Q9, 2005).
- Risk Evaluation: The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk (International Council for Harmonisation Q9, 2005).
- Risk Identification: The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description (International Council for Harmonisation Q9, 2005).
- Risk Management: The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk (International Council for Harmonisation Q9, 2005).
- Risk Reduction: Actions taken to lessen the probability of occurrence of harm and the severity of that harm (International Council for Harmonisation Q9, 2005).

- Risk Review: Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk (International Council for Harmonisation Q9, 2005).
- Severity: A measure of the possible consequences of a hazard (International Council for Harmonisation Q9, 2005).
- Trend: A statistical term referring to the direction or rate of change of a variable(s) (International Council for Harmonisation Q9, 2005).
- State of Control: A condition in which the set of controls consistently provides assurance of continued process performance and product quality (International Council for Harmonisation Q10, 2008).
- Statistical Experimental Design: Is the strategy of organizing experiments in such a way that the information investigated is obtained as efficiently and accurately as possible with the minimum number of experiments. It is a definite way in which an experimental program is to be conducted and concerns the choice of the levels of factors and their combinations to be included in the experiment (Barker, 1985; Lewis et al., 1999; Politis, 2010).
- Variability: It is a measure of fluctuation of the quality characteristics of a product and the result of the influence of all the factors that affect the process that produces it. Quality is inversely proportional to variability. Thus, quality improvement is the reduction of variability in processes and products (Montgomery, 2013). Experimental design is an effective tool of identifying and limiting the sources of variability in a process.

I.2.3. Historical Background

Experimental design is closely connected to quality as it is a tool for product and process understanding and subsequently, ensuring quality. Quality has been identified and expressed in various ways through the years, from ancient times until today. The following figure depicts the path of quality overtime (Georgaki et al., 2010).

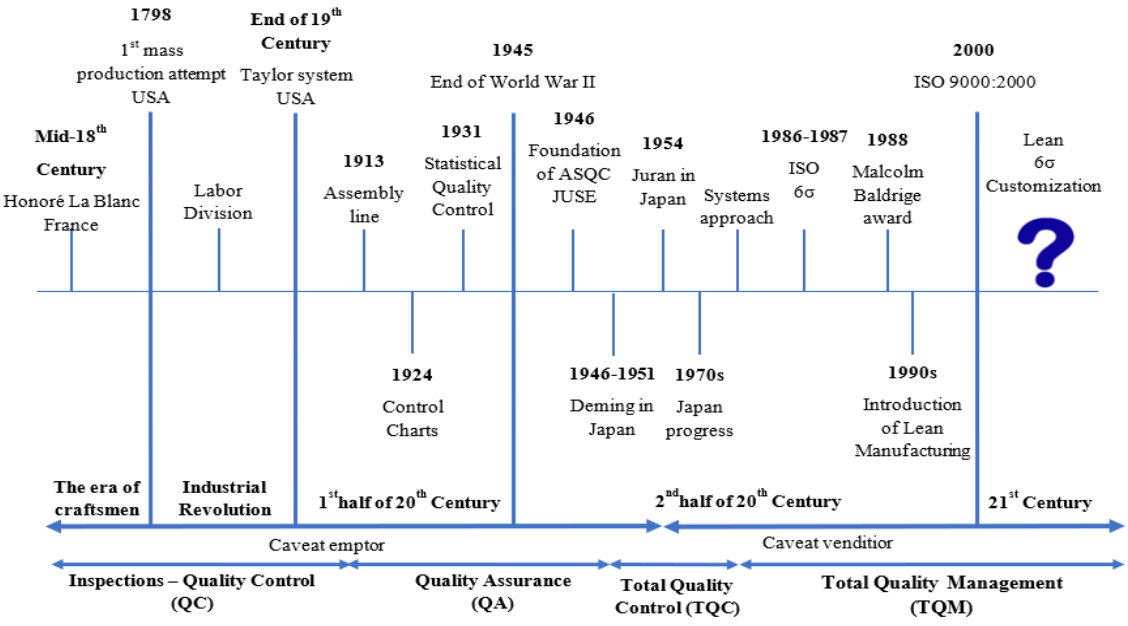


Figure I.2.3: Quality overtime (Georgaki et al., 2010).

During the craftsmen era, in Europe, the craftsmen's' role was to be producers, manufacturers as well as inspectors-auditors and quality was based on intuition and senses, thus quality could not be defined. Even though craftsmen were acting as auditors, the responsibility of quality lied on the buyer, defined as '*caveat emptor'*. In the mid-18th century, Honoré Le Blanc in France invented a system of weapon construction by combining prefabricated parts, a system that later on influenced USA and was the base of the 1st mass production attempt and the precursor of the industrial revolution (Georgaki et al., 2010).

During the industrial revolution, a demand of quality control was necessary as still standardized raw materials and processes were not in use, thus a lot of variability existed. The next step was done by Adam Smith who divided the overall labor to individual tasks and achieved an increased productivity. At the end of the 19th century, USA adopted the Taylor System, according to which, the design of manufacturing is done by the management along with the production engineers, while the workers and supervisors perform the production. Even though this system increased productivity, it was costly as the quality control was based on numerous mass inspections and rejection of faulty products (Georgaki et al., 2010).

The 20th century brought the definition of process and quality at manufacturing and the shift from mass inspection to statistical thinking. Characteristic of this era was the introduction of the assembly line, in-process controls and self-audits by Hendry Ford, the statistical methods and experimental design by organizations like AT&T, Bell and General Electric as well the control charts, invented by the father of Statistical Quality Control, W.E. Shewhart (Georgaki et al., 2010).

After World War II, the American Society of Quality Control (ASCQ) and the Union of Japanese Scientists and Engineers (JUSE) were founded. One of the most important representatives of this era is W. E. Deming, who taught the statistical thinking to the Japanese industry. Representatives of the Japanese statistical progress was G. Taguchi, who started developing experimental design techniques, and K. Ishikawa who established the Cause-and-Effect diagram. At the same time in the USA, V. Feigenbaum and J. M. Juran were the two main representatives with their work based on Total Quality Control and the responsibility of management on quality. The systems approach was also developed at that time.

During the 1970s, Japan managed to get access to the Western market as their products had increased quality compared to USA and until the 1980s the value of quality was recognized by both the consumers and the policy makers. Thus, the caveat emptor shifted to caveat venditior, meaning that the producer has the responsibility of quality. During this decade, the concept of Total Quality Management started to evolve. The recognition of the significance of quality was established by the Malcolm Baldridge National Quality Award in 1988 (Georgaki et al., 2010).

In the next decade, ISO standards were adopted, which were evolved by 2000s. In 1986, the Six Sigma methodology was introduced by Motorola while in the 1990s Toyota developed Lean Manufacturing and Lean Thinking in general, concepts that are applied until today.

The dawn of the 21st century has brought digitalization, affecting the relationship between manufacturer and customer. The organizations of the 21st century need to evolve in such a way that they do not only satisfy the needs of the customer, but they are fast and flexible, corresponding immediately to the customized needs of the customer (Georgaki et al., 2010).

I.2.3.1. Quality Gurus

The main representatives of quality and subsequently of experimental design are divided in three different timeframes. Table I.2.1 depicts the quality gurus, their key phrase, and main contributions.

Table I.2.1: Quality Gurus, their key phrase and their main contribution (Georgaki et al., 2010).

Time period	Quality Guru	Key Phrase	Main Contribution
1st American Wave (until the 1950s)	W. A. Shewhart	Objective & Subjective Quality	Control Charts, Statistical Quality Control
	W. E. Deming	Customer focus	Seven Deadly Diseases, 14 Points for Management, System of Profound Knowledge
	J. M. Juran	Fitness for Use	Fitness for Use, Juran Trilogy, Cost of Quality
	A. V. Feigenbaum	Customer Satisfaction	Total Quality Control, Cost of Quality
The reaction of the Japanese (from 1950 onwards)	K. Ishikawa	Insufficient Compliance with the Specifications	Cause & Effect/ Fishbone Diagram, Quality control throughout the whole organization, Quality Control Circles, Kaizen (continual improvement)
	G. Taguchi	The reverse of loss	The loss function, Robust designs
	S. Shingo	Zero defects are entirely possible	Zero Quality Control, Poka Yoke, SMED System
	M. Imai	On demand production	Kaizen (Improvement), Gemba Kaizen (on-site improvement)
The New West Wave (from the 1970s onwards)	P. Crosby	Quality is Free	Zero Defects, Do it right from the beginning or Do it Right from the First Time, Quality Vaccine
	J. S. Oakland	Doing the Right Things Right	Total Quality Management, Quality Chains
	D. A. Garvin	Understanding of Quality	Eight Dimensions of Quality, Five Approaches to Quality, Learning Organizations
	T. Peters	Simplification of design, manufacturing, processes, and procedures	Leadership - Innovation - Human resources - Customers
	C. Møller	The Human Side of Quality	17 Quality Standards
	R. M. Pirsig	I'm stupid about Quality	Metaphysics of Quality

W. A. Shewhart

Shewhart argues that quality has an objective and a subjective dimension. The subjective dimension is the assessment of how good a product is and has as a measure the satisfaction of a need. Measuring the objective dimension of quality is both possible and necessary, so the use of quality standards is essential. But what adds commercial value is the subjective perception. Therefore, the first step to achieve quality is the expression of the customer's needs and their expression in measurable characteristics of the product, i.e., in specifications. The second step is the development of product production processes, the deviation of which from the specifications, i.e., variability, will be only due to accidental causes.

Shewhart aimed to develop a data presentation method to separate the causes of variability that affect a process. There are two types of variability, random, due to occasional-random causes, and systematic variability, due to specific-systematic causes. In order to separate these causes, he developed the Control Charts, which are his most important contribution. Control charts are a technique widely used to detect in real time the occurrence of specific causes of variability in a process (on-line process-monitoring). We can monitor the average value and the variation (or standard deviation) of the quality characteristic through random samples from the products produced. When the sample points are within control limits but behave in a systematic or non-random way, then this is also an indication that the process is out of control. The most basic forms of non-random patterns of behavior of a series of points are the patterns of cycles, mixtures, shifts in the process level, the patterns of trends and the patterns of lack of variability (stratification).

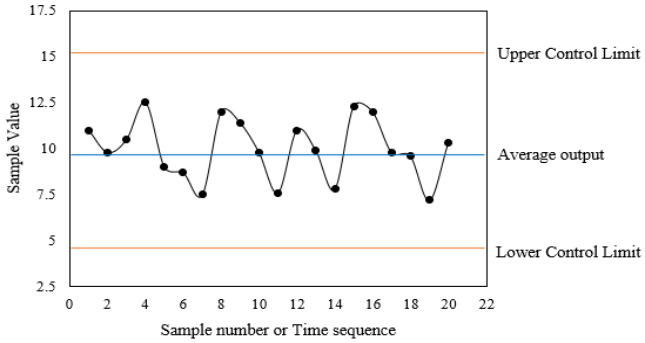


Figure I.2.4: Control Chart example.

Another Shewhart contribution is the Shewhart cycle, which formed the basis of the PDSA cycle or Deming cycle and is characterized as "the act of control". The cycle includes three stages. The first concerns the determination of the desired purpose, the second the effort to achieve this purpose and the last, that of control, it is judged whether the purpose has been achieved.

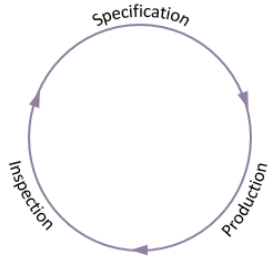


Figure I.2 5: Shewhart cycle

W. E. Deming

What characterizes Deming is the respect he indicates to the human factor and the recognition of the contribution of each employee, no matter how low he is in the hierarchy. Following Shewhart's views, he understands the existence of variability and considers it fundamental to distinguish between random and systematic causes of variability. Any effort to improve quality must be to reduce variability by removing systematic causes even during the design phase. Reducing variability and eradicating systematic causes will lead the system to stability, i.e., statistical control, with many advantages such as stabilizing the process with predictable performance, capability and cost, uniformity in outputs without delays, maximizing productivity while minimizing costs and ease of measurement of the impact of changes on the system. However, statistical control is not enough, because a process may be under control and still produce defective products. When it turns out that the processes are capable, i.e., they are under statistical control and produce products within the specifications, then it only makes sense to start activities to improve quality.

The PDSA cycle is a simple and systematic problem-solving methodology, through which continuous quality improvement can be achieved. The cycle includes four stages, PLAN-DO-STUDY-ACT hence PDSA.

PLAN: Study the current situation and data, identify problems, identify goals and priorities, define the processes that follow, identify incoming-outgoing, customers, data collection, design and develop methods of action.

DO: Trial implementation of the project developed in the previous stage on a pilot scale. Collection and monitoring of results.

STUDY: Study and evaluation of results, assessment of whether the test design is correct and whether modifications are required. Troubleshooting and proposing a new action plan if needed. This stage was added by Deming, wanting to show the value of knowledge.

ACT: Adopt or reject the previous plan. Stabilize the process and prepare for the next improvements.

With the completion of the last stage the cycle returns to the design stage in order to identify new opportunities for improvement. So, the cycle does not end, but instead is a methodology for continuous improvement. It is based on the application of knowledge and decision-making based on facts and not on arbitrary conclusions, elements that Deming supports in the Profound Knowledge System.

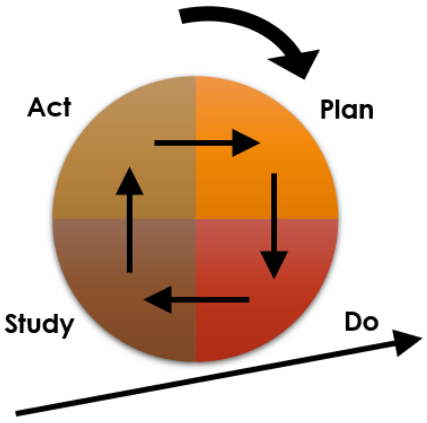


Figure I.2.6: Deming's PDSA cycle.

Deming's most important contribution is the 14 Points for Management, providing the principles for radical reform of the organizations and the administration, as a starting point for the improvement of the quality and the productivity. This presupposes the full commitment of the administration and the participation of all. In contrast, the 7 Deadly Diseases of management describe the resistance that an organization encounters in its quest to achieve quality. Deming's views and the spirit of the 14 Points for Management are summarized in the Profound Knowledge System and include the necessary knowledge required for the transformation of management. This knowledge is developed in four axes: Focus on the System, Understanding of Variability, Theory of Knowledge, and Psychology.

J.M. Juran

Juran got involved mainly with quality management. Defines quality as "Fitness for Use", thus emphasizing the need to comply with specifications, which however is only one means of achieving the goal, which is customer satisfaction. Specifications are benchmarks, but quality is a moving goal.

Juran observed the uneven distribution in the frequency of defects, i.e., although there were many types of defects, a relatively small number of them occurred more frequently and was responsible for the majority of defective products. This phenomenon was named as the '*Principle of the vital few and trivial many*' or as the '*vital few and useful many*' and was associated with Pareto's work giving the name '*Pareto Principle or Beginning 80-20'*. The Pareto diagram, one of the seven basic tools of quality control, is based on this principle.

The Juran trilogy is a comprehensive proposal for quality management and includes three sub-processes, Design, Control and Quality Improvement. The three parts of the trilogy are interrelated as shown in the diagram of the Juran Trilogy. At the design stage, customers and their needs, goals, products, and processes are identified. The production department executes the processes and produces the products, however, as the process progresses, it turns out that it is not capable of producing 100% satisfactory product. About 20% of the work must be repeated due to defects. This loss occurs for years because that is how the process was designed and therefore quality problems have been incorporated into it from the design phase. If management is conservative, they will try to control the quality with *After the fact inspection* to avoid occasional outbreaks of poor-quality costs. Conversely, if improvement plans are implemented, after a period of time the losses are reduced and the process will be at an improved level of control, which corresponds to a lower cost of poor quality.

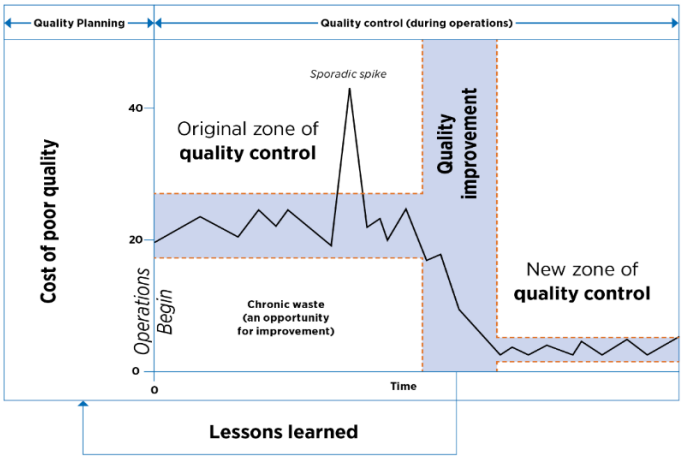


Figure I.2. 7: Juran Trilogy Diagram (Juran, 1986).

A.V. Feigenbaum

Feigenbaum's name is associated with the concept of Total Quality Control. According to him, Total Quality Control is an effective system in order to unify the efforts for development, maintenance, and quality improvement by various groups within an organization, in order to favor the availability, the mechanical design, the production and the provision of services. in the most economical way, which allows complete customer satisfaction. Total Quality Control enters all phases of the industrial cycle, from the design to the delivery to the customer of a product that satisfies him. This can only be done with the correct production from the beginning and with prevention. So quality is not a matter of control, but the result of the contribution of all the staff and departments of an organization.

According to Feigenbaum, quality is influenced by Nine Fundamental factors, the "*9 M*", which are:

Market – Money – Management – Men – Motivation – Materials – Machines/mechanization – Modern information methods – Mounting product requirements.

Feigenbaum developed the concept of Cost of Quality. It is a measure associated with the achievement or failure of quality products or services. Includes: prevention costs, assessment costs and failure costs. The cost of prevention is the cost of all specially designed activities to prevent the occurrence (e.g., supplier evaluation, quality training, quality teams, etc.). Estimation costs relate to the measurement, evaluation, or inspection of products/ services to ensure that they comply with the specifications (e.g., control of raw materials, intermediate and final products, process inspection, maintenance, adjustment of equipment). Failure cost is the cost that occurs when non-compliant products are detected, which either have not been delivered to the customer, then we are talking about internal failure cost, or have reached the customer and then we are talking about external failure cost (e.g., reprocessing- re-examination, complaint management, returns, loss of customer loyalty). Total quality cost is the sum of the above cost categories and expresses the difference between the actual-existing cost of a product and the ideal cost that a product would have if there was no defective product or if there were no production problems or if there was no need for quality controls etc.

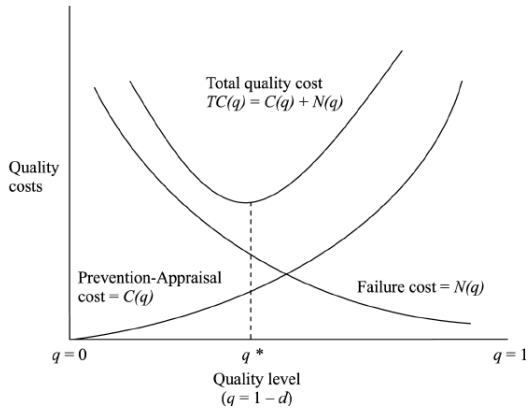


Figure I.2.8: Cost of Quality by Feigenbaum.

K. Ishikawa

Ishikawa, like Deming, emphasizes that management has all the responsibility and must be fully committed to demonstrating quality. At the same time, however, the participation of all employees of each department of the organization is necessary to create a unified system. This unified system by using a variety of

techniques such as statistical and technical methods, standards and regulations, computational methods and automated controls can achieve Quality Control throughout the organization, i.e., Total Quality Control. In this way, products and services can be produced with the optimal cost-effectiveness and utility, which the customer will buy with satisfaction.

One of Ishikawa's most important contributions is the "C*ause and Effect diagrams or Fishbone or Ishikawa diagrams"*. These diagrams show the relationship between a given result and the causes that contribute to it. Thus, they are a useful tool for collecting and organizing causes, the common understanding of a problem and the study of each cause separately. This diagram includes the six basic categories of appearance of an effect, the so-called 5M + E, which consist of "*Measurements, Materials, Machines, Methods, Man-Power and Environment*".

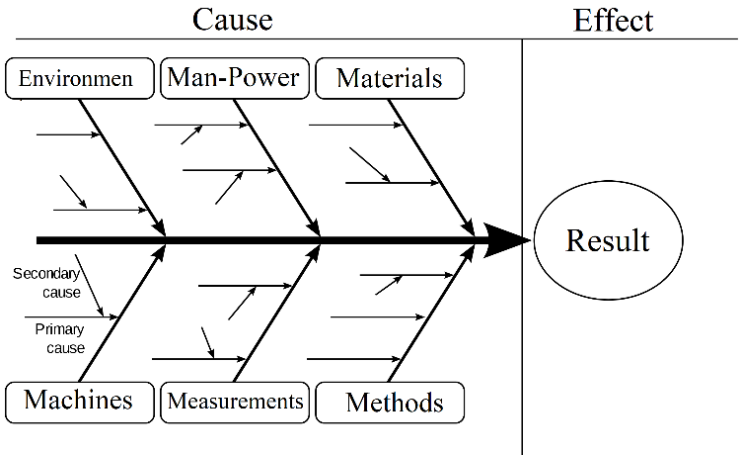


Figure I.2.9: Cause and Effect diagram or Fishbone or Ishikawa diagram.

Ishikawa was the first to categorize quality control techniques according to their degree of difficulty into three categories and assembled the Seven Basic Tools of Statistical Control.

Table I.2.2: Separation of Quality Controls Techniques

Seven Basic Tools of Statistical Control	Statistical Tools of Intermediate Difficulty	Advanced Statistical Tools
Control Sheets	Sampling theory	Advanced Experimental Design
Graphs	Inspection by Sampling	Multivariate Analysis
Histograms	Statistical Conclusion - Hypothesis Testing	Operational Research
Pareto diagrams	Design of Experiments	
Cause-Effect Diagrams		
Dispersion Charts		
Quality Control Charts		

G. Taguchi

Taguchi is mainly interested in optimizing products and processes before production instead of trying to achieve quality through inspections. Considers that quality efforts should focus on the design phase. He defines quality through the concept of loss and considers that simple compliance with the specifications is not sufficient. Using the loss function, Taguchi assigns a numerical target value to the attribute in question. The closer the value of the attribute is to the target, the lower the variability, the smaller the damage. Using the quadratic equation, it correlates the damage with the deviations, so the greater the deviation from the target value, the greater the damage.

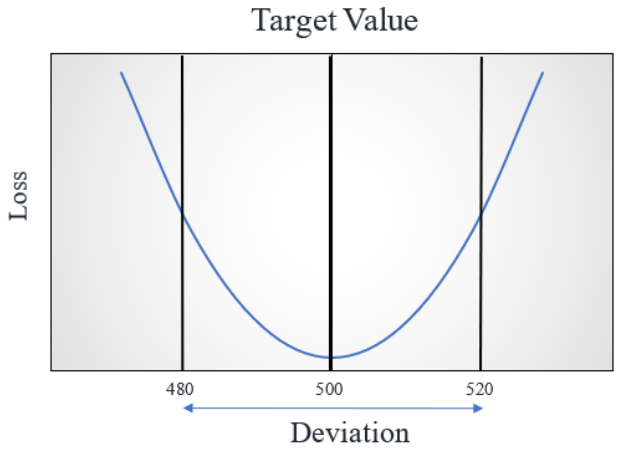


Figure I.2.10: The Taguchi loss function.

The robust design is characterized by the technique of appropriate selection of control variables, in order to limit the sensitivity of the product to variability. The central idea is that in addition to the control variables, the noise variables must also be considered.

S. Shingo

Shingo devised a system and a broader approach to preventing errors based on inspection at the source. This is possible by monitoring the processes through appropriate mechanical equipment that ensures the immediate feedback of the information. Thus, it has the ability to provide information about the prevailing conditions and whether they can ensure the desired quality before the start of the production process.

Inspection at the source is characterized by the fact that the production process can be stopped as soon as an error occurs. This is followed by its recognition and the prevention of its recurrence. In this way the error is recognized at the source and its transformation into a defect is avoided, without the need to result in statistical sampling. This is the core of Zero Quality Control, which is based on Poka-yoke devices. Poka-yoke (error-proofing / mistake-proofing) device is any mechanism that prevents an error from occurring or makes the error immediately apparent. These devices prevent the employee from committing errors and thus save time from inspections, which can be allocated to areas such as identifying their causes. The zero defects approach can be realized with the use of such devices.

Shingo also developed the SMED system, Single Minute Exchange of Dies, which reduces the dead time for the settings and changes of the machines between two consecutive productions, in the framework of the Just in Time approach. It is a system of organization and production management that allows the rapid production of even small batches while reducing inventories.

M. Imai

Imai's work is summarized in two terms: Kaizen & Gemba Kaizen, which means gradual, continuous improvement, i.e., the change for the better.

According to Kaizen's approach, improvements affect all areas of a business, i.e., reducing costs, developing employee skills, meeting deadlines, etc., and require the involvement of all employees. Kaizen should be a way of life and not a trend. His approach is anthropocentric and includes the improvement of the person in personal, social, and professional level. Also, Kaizen is not based on sudden and abrupt changes but on small, gradual, and continuous improvements, constantly setting small goals. These changes are made at little or no cost, as they do not depend on the purchase of new equipment but on the better utilization of already available resources. In addition, Kaizen supports the elimination of unnecessary processes that do not add value and the avoidance of waste or muda as it is called. For all this to happen it requires a very good familiarization with the workplace, as Kaizen cannot be done from an office but in the production area. Gemba means real space and describes the space in which the action takes place. So Gemba Kaizen means continuous improvement that takes place in the real field of action. These concepts are related to concept of Lean Manufacturing and the shift From Push to Pull.

P. B. Crosby

Crosby's name is associated with the "*Zero Defects*" approach and "*Do it right from the beginning*" or "*Do it right from the first time*". He describes zero defects as a standard of performance or a prevention strategy, which is associated with the mentality of doing it right from the beginning.

For Crosby quality is compliance with the specifications set by the manufacturer to meet a specific customer need. So, if the system allows deviations from the specifications, it encourages failure. He advocates the prevention and integration of quality from the design phase and opposes attempts to achieve quality through inspections.

Finally, Crosby talked about the "*Quality Vaccine*" which is a method of preventing poor quality and the basis for improving it. It includes three stages:

- Determination: Recognizing that quality improvement is essential for the growth, prosperity, and survival of an organization.
- Training: All employees of the organization must understand their role in the quality improvement process.
- Application: The implementation of the quality improvement process is a matter of communication and activities and does not require additional people or equipment.

J.S. Oakland

Oakland is one of the few European quality scholars. His work concerns Total Quality Management, which he considers as the necessary way of managing an organization to ensure complete customer satisfaction. He emphasizes on prevention, systems theory, and customer satisfaction.

Oakland has developed a total quality management model, as shown in Figure I.2.11. According to this model, improved Planning, People Management and Processes can increase Performance. These four concepts (4P) are the foundations for the delivery of quality products and services to the customer and are the "*hard management necessities*" in total quality management. In between, the three "*soft outcomes*" (3C)

exist: the Commitment to quality and the satisfaction of the customer's needs, the Communication and spread of the message for quality and the recognition of the need to change the mentality of the organization in order to achieve total quality, thus change the Culture of the organization (Oakland, 2014).

Figure I.2.11: Oakland's "4Ps & 3Cs" framework

Oakland also talked about quality chains, that is, sequences of internal suppliers and customers, which are found throughout the range of organizations. These chains can break at any point when a person or machine does not meet the specifications set by the customer, internal or external. However, this failure becomes apparent at the interface between the organization and the external client.

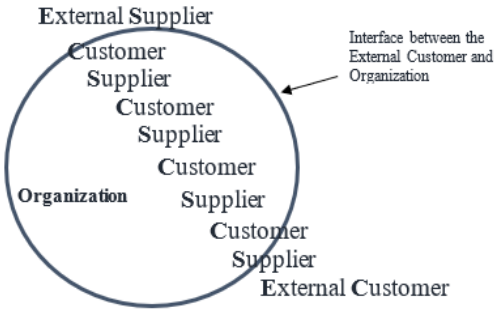


Figure I.2.12: Quality chains

Finally, Oakland is opposed to the dependency on quality controls or inspections to achieve quality. Asking the question "Did we do the job right?" quality is not achieved through design to the product or service. Asking the question "Are we able to do the job right?" expresses the ability of processes, i.e., what a process that is statistically controlled can achieve in relation to the specifications. The next question that arises is "Are we still doing the job right?" addressing the need to monitor processes. By asking the right questions in the right order, the need for inspection is weakened and the approach of detecting errors after they are made is replaced by the strategy of prevention.

D. A. Garvin

Garvin believes that quality management requires understanding. But quality has a different meaning for management, employees, or customers. It therefore distinguishes eight dimensions of quality and five approaches to quality. The eight dimensions of quality according to Garvin are:

- Performance: Will the product fulfill its intended purpose?
- Features: What else does the product do or have?
- Reliability: How often does the product or service fail to do what is supposed to do?
- Durability: Which is the shelf life of the product?
- Serviceability: How easy can the product be repaired?
- Conformance to Standards: Does the product comply with the specifications?
- Aesthetics: How does the product look like?
- Perceived quality: What is the reputation of the product, service, or organization?

Other dimensions of quality that are distinguished are:

- Safety: How safe is the product?
- Availability-Access: How easy is it to access the product or service?
- Price: Does the price of the product correspond to its characteristics?
- Ergonomics- User Friendliness: How easy-to-use is the product?

Garvin has identified five approaches to quality that express how quality is defined.

- Quality can be a matter of judgment or, as Shewhart put it, the subjective perception of quality expresses how good the product is. This is the transcendental view of quality, meaning exceeding the limits. In this case the quality is universally perceived but cannot be defined. It is perceived when one sees it.
- Quality can be defined in terms of the product. Performance, reliability, price, additional features, etc. are the dimensions of quality associated with the product.
- Quality can be determined by the customer. Satisfaction, suitability for use, aesthetics, and perceived quality concern the relationship of the product with the customer.
- Quality can be expressed in terms of the producer/manufacturer, so quality is compliance with specifications, limitation of variability or standardization to ensure the same level of customer service.
- Quality can be determined on the basis of value, meaning the relationship of quality to the value one receives from use and the price one is required to pay (Value for money).

Finally, Garvin strongly argues that in order for organizations to remain effective, they must encourage and support learning. According to Garvin, a learning organization is an organization that has the ability to create, acquire, and transmit knowledge, and to modify its behavior to reflect new knowledge and perception.

T. Peters

Peters develops his ideas on four aspects: Leadership-Innovation-Human Resources-Customers.

He condemns bureaucracy, mediocrity, and business inaction, while he applauds the individual's contribution, initiative, creativity, and innovation. He emphasizes the central role of leadership in any effort to improve quality and believes that management should be managed “by walking”, because in this way it comes in contact with employees, customers, and processes of the organization, having the opportunity to listen, advise and assist employees in their workplace (gemba kaizen - muda walks).

Peters also mentions the value of both attracting new customers and retaining existing ones. To achieve this, the organization must aim to respond immediately to the needs of the customer but also to pleasantly surprise him. He emphasizes that failure is caused either because there is passion but there is no system, or because there is a system but there is no passion.

Finally, he analyzes the need for simplification of processes and elimination of unnecessary stages, in order to reduce bureaucracy and simplify the structure of the organization. An organization must be flexible and have few levels of management.

C. Møller

Møller introduced another dimension to quality, the human. To meet the needs of the customer, organizations and employees must have the inspiration for the best, something that can be achieved by the improvement of the individual and the change of mentality. For Møller, personal quality is the basis for achieving any dimension of quality. In personal quality there are two levels, the level of ideal performance and the level of real performance. The first is the personal quality goals of the individual, influenced by his experiences and determines the development of the individual and his capabilities. The second level is determined by the individual's self-confidence and the degree of approach to the ideal performance level. Actual performance is influenced by factors such as subject knowledge, experience and skills, recognition, or reprimand.

In terms of quality in organizations, Moller has identified 17 quality features. Some of these are the emphasis on quality development, management involvement, customer satisfaction, investment in training, dedicated employees, and error prevention.

R. M. Pirsig

Pirsig's ideas are not directly related to those of the classical scholars of quality, as his work is philosophical and literary and mainly focuses on the connection between science, spirituality, and ethics. However, in his books there are concepts such as system, innovation, quality education as well as the connection between quality and value.

Pirsig refuses to define quality, so the distinction of quality between objective and subjective does not make sense because it is still an attempt to give a definition to a concept that he considers cannot be defined. The refusal to define quality does not, however, preclude its existence. By showing that the world cannot function normally without quality, it confirms its existence. Pirsig has also referred to the metaphysics of quality.

I.2.3.2. The Evolution of Quality

The evolution of quality throughout the years and inputs of the quality gurus is depicted in Figure I.2.13. Quality has evolved from simple inspections to the use of engineering principles to "build" quality into the product, the so called in the later Guidelines, "Build in Quality" (Korakianiti and Rekkas, 2011). From Shewhart, who was the first to introduce statistical tools to identify process variability and relate it to product quality, to Deming who highlighted the statistical process mapping and proposed a systematic approach for continuous improvement and to Juran who also, mentioned the responsibility of management in preserving and improving quality, industry quality has gradually shifted from random testing to Quality by Design (QbD).

Initially the quality control was based on the testing of each unit for compliance with the specifications. Due to the exhausting testing, the acceptance sampling was adopted. Thus, during this period, the guiding principle of quality control is inspection. Subsequently, the Japanese quality gurus were the ones to bring industry quality one step further and shifted from quality control and testing of the final product to quality assurance by implementing preventive actions, "*From find and fix or reject to Prevent*" (Korakianiti and Rekkas, 2011). This spread throughout the organization and the concept of Total Quality Management, and the holistic aspect of quality was born through the quality gurus Feigenbaum, Oakland etc. Quality is not focused only to manufacturing but to the hole organization through management and employees with the use of quantitative methods to achieve continuous improvement.

In short, quality has evolved by shifting from product focus to process and systems focus.

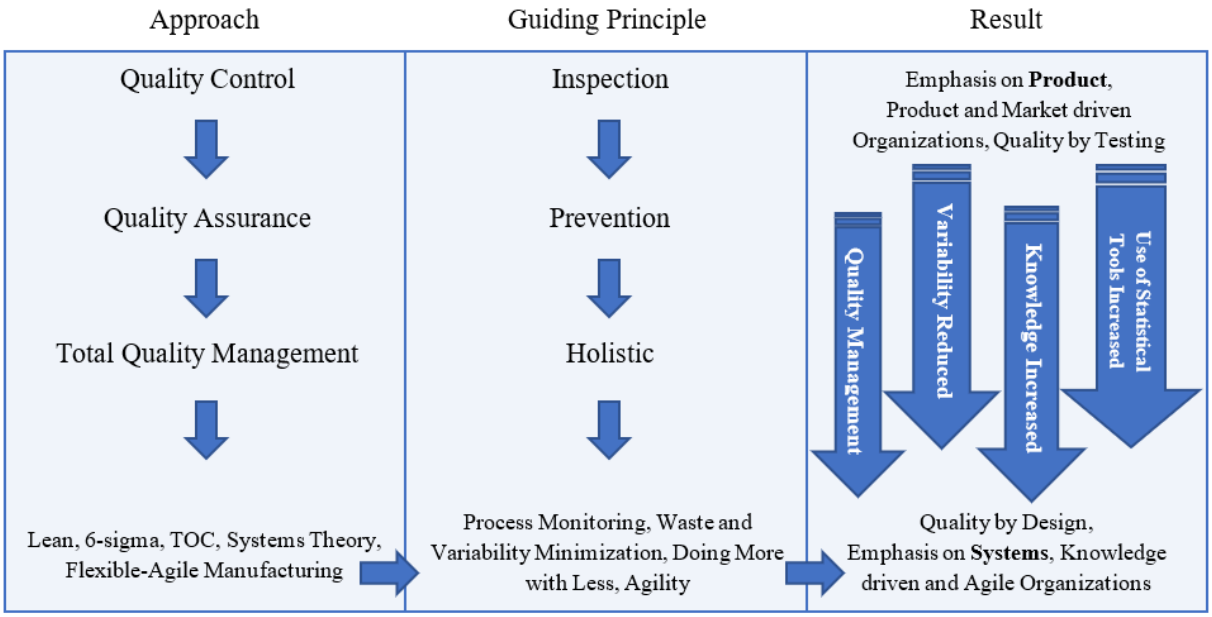


Figure I.2.13: Major Milestone in Evolution of Quality (Korakianiti and Rekkas, 2011).

I.2.3.3. Modern Approaches to Manufacturing

The evolution of quality has led to the use of modern manufacturing methods which are based on the deep knowledge of the processes and the product characteristics and how these attributes interact. It is worth mentioning three main methods currently used by the modern manufacturing industry, "Lean Manufacturing", "Six-Sigma" as well as the "Theory of Constrains". The adoption of the above approaches leads to continuous improvement of quality, increased agility, improved response to customer needs, innovation, and reduction of costs (Politis, 2010).

Lean Manufacturing

Lean Manufacturing, also known as "Just in Time" or "One Piece Flow" is directly related to the Kaizen, gemba kaizen and muda concepts described. According to lean manufacturing, in a process e.g., step 1 should not produce a piece if step 2 has not used the pieces that step 1 originally produced. Meaning that, production is determined by the demand of the last step of the process and this demand is successively

transferred to the first step. The next step activates immediately the preceding one with a signal. In this way each step recognizes what, when and how much it will produce to meet the demand of the next step, while also activating the previous step. Thus, production is adjusted according to demand, which is characterized as "Pull" and thus overproduction and stocks are prevented (Georgaki et al., 2010).

Lean production opposed to mass production. Mass production is not determined by demand but pushes the product to the customer based on forecasts for future demand, which in turn are based on past sales. This favors the production of defective products, which require mass inspection and control to be detected. In contrast, in lean manufacturing and generally in lean thinking, production is determined by real demand, i.e., by the next stages of the processes and in final analysis of the customer, in order to have delivered what he needs at the moment and in the quantity, he needs it. This ensures a smooth flow of the product produced at all stages of the process and prevents mass production and waiting (batch and queue). The aim is the continuous flow of product units (One Piece Flow), the avoidance of stocks and in general the elimination of any kind of waste. Also, in lean manufacturing the process stops when a problem arises and its immediate correction is sought so that the next process never accepts defective products, while the continuous exploitation of the knowledge gained from these interventions leads to improvement.

The potential weakness of lean production lies in the consequences of limited inventories, i.e., in the event that production is stopped, demand will not be able to offset, which can be avoided in mass production.

It is obvious that lean manufacturing requires good knowledge of the process, which can be acquired by the application of experimental design. During development phase, experimental design can offer the deep knowledge of the process and the identification of the sources of variability. In combination with total quality management, an organization can be led to lean manufacturing and continuous improvement. Benefits such as increased productivity, elimination of waste, improved quality, decreased lead time, product flow and space release (Politis, 2010).

6 Sigma

6 sigma is an intensive and systematic methodology for the application of known and effective quality tools and techniques. Combining cognitive items from the field of quality, 6 Sigma aims to improve quality by eliminating variability, which is due to defects that negatively affect customer needs, emphasizes the characteristics of the product that are critical and therefore satisfies the customer.

The name 6 Sigma comes from the Greek letter σ which symbolizes the standard deviation and is an indicator of the variability of a process. The number 6 expresses the ability of the process under statistical control to meet the specifications, which corresponds to a probability equal to 99.9999998% (Georgaki et al., 2010).

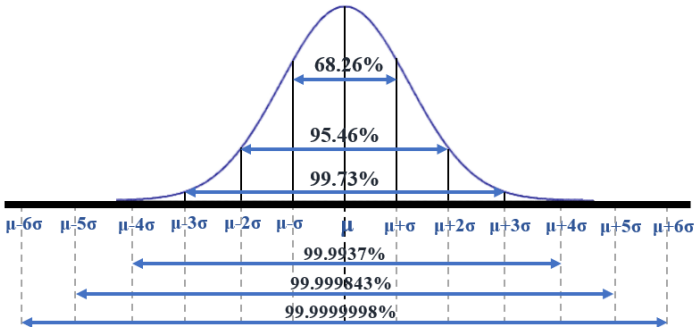


Figure I.2 14: 6-Sigma Approach.

In 6-Sigma approach, the performance of a process is expressed in defects per million chances of a defect or non-compliance occurring (DPMO). Defects per million opportunities are calculated from defects per unit. In practice, the 6 Sigma (6σ) represent a quality level that yields no more than 3.4 defects per million opportunities. In theory, however, at level 6σ the percentage of prices between the 6σ corresponds to 99.9999998% of the total, so only 2 defects per billion opportunities would be expected. This difference is due to the fact that the average value of the process is shifted 1.5σ across the center because the processes are not static but dynamic.

In practice, organizations operate at level 3σ, in industry ("industry average") 4σ are often achieved, while service organizations operate at level 1σ or 2σ ("noncompetitive"). The 3σ correspond to 2700 DPMO which is generally a good performance (0.27% chance of being outside the 3σ limit). However, the greater the number of stages of a process or parts of a product, the greater the likelihood that the final product will be defective.

The basic tool for the application of 6 Sigma is the DMAIC model which includes the following stages:

- Define: Define the process, customers, inputs and outputs, the current status and the goal of improvement.
- Measure: Measure the system, apply reliable methods for process monitoring and collect data.
- Analyze: Analysis and evaluation of the collected data and the system, identification of the causes of defects.
- Improve: Improve the process and the system, application of solutions, validation of improvements.
- Control: Control of the new system, standardization of the system in case the improvements were successful and monitoring of the new system.

Theory of Constrains

Theory of Constrains was introduced by E. Goldratt, who describes systems as chains or networks of chains. The performance of a system is determined by the weakest link. Therefore, no matter how much effort is made to improve system processes, substantial improvement will only occur if improvements are made to the weak link. The weak link is the limitation of the system.

The application of Theory of Constrains includes five focusing stages:

- Identify: Identify the current constraint (the single part of the process that limits the rate at which the goal is achieved)
- Exploit: Make quick improvements to the throughput of the constraint using existing resources (i.e., make the most of what you have).
- Subordinate and Synchronize: Review all other activities in the process to ensure that they are aligned with and truly support the needs of the constraint.
- Elevate the performance of the constraint: If the constraint still exists (i.e., it has not moved), consider what further actions can be taken to eliminate it from being the constraint. Normally, actions are continued at this step until the constraint has been "broken" (until it has moved somewhere else).
- Repeat the process: The five focusing steps are a continuous improvement cycle. Therefore, once a constraint is resolved the next constraint should immediately be addressed.

The Theory of Constraints emphasizes to continuous improvement and the avoidance of inaction after achieving the goal. This methodology is effective in terms of reducing product transit time through processes, reducing waste and variability, and improving quality.

The Theory of Constraints includes a sophisticated problem-solving methodology called the Thinking Processes. The Thinking Processes are optimized for complex systems with many interdependencies (e.g., manufacturing lines). They are designed as scientific "cause and effect" tools, which strive to first identify the root causes of undesirable effects and then remove them without creating new ones. The Thinking Processes are used to answer the following three questions, which are essential to Theory of Constraints:

- What needs to be changed?
- What should it be changed to?
- What actions will cause the change?

Combination of the modern approaches

The combination of Lean Manufacturing and the 6-Sigma with the Theory of Constraints enriches the first two methodologies with the understanding of the system that is necessary for the substantial improvement, while it helps to identify the priority on the basis of which the various problems must be solved. The three methodologies are not mutually exclusive but complement each other and are modern extensions of Total Quality.

Table I.2.3: Target, strategy, advantages, and disadvantages of modern approaches to manufacturing.

Methodology	Lean Manufacturing	6-Sigma	Theory of Constraints
Target	Limitation of waste and processes that do not add value to the product	Limitation of Variability	Removal of restrictive steps
Strategy	1. Determination of value 2. Transit of value 3. Flow improvement 4. Pull 5. Perfection	1. Determination 2. Measurement 3. Analysis 4. Improvement 5. Control	1. Define 2. Exploit 3. Subordinate 4. Elevate 5. Repeat
Advantages	• Review of the way the organization works. • Maintain only value-added processes • Involvement of the whole organization • Possibility of immediate correction	• Reliability of statistical methods • Limitation of Variability • Predictability of results, risk reduction	• Indicates the issues that have priority • Total perception of the system • Distinguish between physical and explicit restriction
Disadvantages	• Does not provide for the use of statistical tools – does not exclude them also. • Incomplete view of the system	• Individual process improvement without appreciation for the system • Non-participation of the whole organization	• Does not provide for the use of statistical tools • It is not enough on its own to change the organization's mentality • Eliminating constraints does not mean eliminating waste

Modular Manufacturing

Modular manufacturing is an innovative way of industrial production which enables the industrial installation to be "disassembled" into independent, functional units (modules), which are manufactured separately and then assembled together in its final installation site. Thus, the simplification-standardization of the processes is allowed, as well as the reuse of plans or even the units themselves in different future installations. These detachable modules can easily be "cloned" or used for new, innovative productive needs, which require significantly less productive resources. Therefore, modular manufacturing provides great flexibility, as it allows faster construction and installation of modules and at the same time their easy modification or transfer. In addition, it is possible to produce multiple products due to faster transition times, while reducing production costs. Producers who aim to respond quickly to market demands, to produce a variety of products that require different production schedules in smaller batches, can increase their productivity through this innovative way of production (Riley, 2016).

Continuous manufacturing

Continuous production is a method characterized by continuous flow (flow production method), in order to produce products without interruption. Continuous production is the opposite of batch production, in which the product is produced gradually through a series of steps in successive workstations, presupposing the interruption of production, before the start of the next stage and the next batch. Therefore, these waiting times do not add value to the final product and create the conditions for waste and loss of resources (Hernandez, 2015). The word "continuous" usually means that the machines are capable of operating on a 24-hour basis, with weekly maintenance breaks scheduled. The idea of continuous manufacturing came from the production of iron using a blast furnace, where the process is carried out continuously for many years. This approach was subsequently adopted by the oil refining, chemical, synthetic, fertilizer, energy, gas, and wastewater industries. The application of continuous production in the pharmaceutical industry has evolved slowly over the last decade. To date, some medicinal products are produced and marketed using continuous production processes (Chaudhary et al., 2017).

In the last year, a draft ICH guidance for industry titled "*Q13 Continuous Manufacturing of Drug Substances and Drug Products*" has been available, describing scientific and regulatory considerations for the development, implementation, and operation of continuous manufacturing (ICH Q13, 2021). This new ICH guidance provides global harmonization for continuous manufacturing regulatory approaches and encourages broader adoption of this technology. This guidance builds on existing ICH Quality guidelines, including ICH Q7 through Q10.

I.2.4. Guidelines

Experimental design as part of the overall concept of Quality by Design (QbD) has become worldwide the main part of all quality guidelines that define the pharmaceutical industry and especially the development of new pharmaceutical products. More specifically, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has established among others, three main guidelines that aim to "*the development of a harmonized pharmaceutical quality system applicable across the life-cycle of the product, emphasizing on an integrated approach to risk management and science"* (International Council for Harmonisation, 2018). These guidelines namely (International Council for Harmonisation):

- ICH Q8: Pharmaceutical development
- ICH Q9: Quality risk management
- ICH Q10: Pharmaceutical quality system

provide high level directions with respect to the scope and definition of QbD as it applies to the pharmaceutical industry (Amidon et al., 2014).

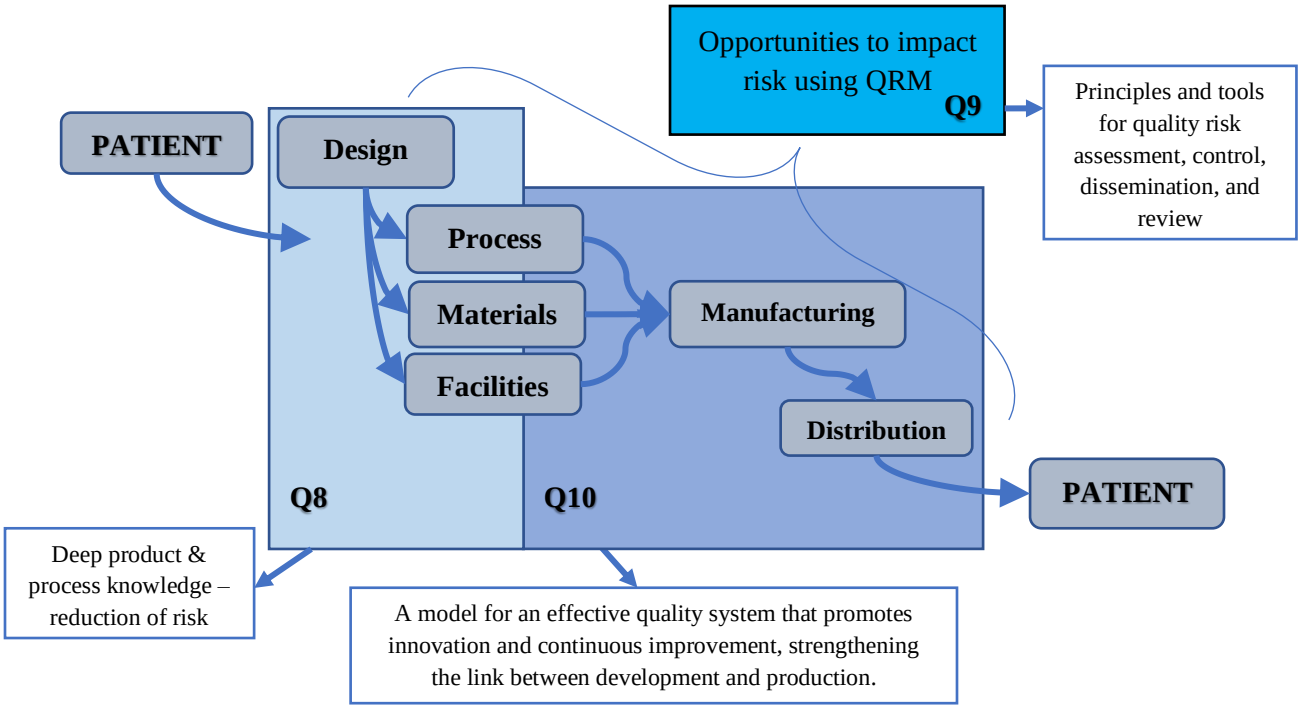


Figure I.2.15: ICH Guidelines Q8, Q9, Q10.

I.2.4.1. ICH Q8 – Pharmaceutical Development

ICH Q8 guideline refers to the development of pharmaceutical products and provides the knowledge and understanding of the product and manufacturing process in order to produce continuously and consistently products of the desired quality and performance. The phrase that characterizes this directive is: *"Quality cannot be tested into products; Quality should be built in by design*" and refers to the knowledge acquired and utilized during the development of pharmaceutical forms so that the manufacturing process and the quality of the product are constantly improved according to the needs of the patient.

The directive specifically states that, when developing pharmaceutical forms, the knowledge gained throughout this step should be described and it should be demonstrated that the type of dosage form chosen as well as the proposed composition are suitable for the intended use. In addition, sufficient information must be provided to understand both the development process of the medicinal product and its production process. Also, the directive focuses on the characteristics and the limits of the active substance, the excipients, the packaging, and the parameters of the process that can affect the quality of the final product. In other words, the critical quality attributes, and the critical process parameters (CQAs and CPPs). Finally, appropriate control strategies for the above characteristics must be developed and justified. All the above mentioned, require deep process and product knowledge that one can gain from the process of developing pharmaceutical forms. An enhanced approach can lead to the opportunity for improved knowledge of

product performance, a higher degree of understanding of the characteristics of the material, production processes and their controls, as well as an expanded design space. The way in which one can gain this enhanced knowledge is through Experimental Design (DoE), Process Analytical Technology (PAT), utilization of prior knowledge and quality risk management, essentially, through Quality by Design (QbD).

In addition to expanded product knowledge and understanding of the production process, the QbD adoption offers more flexible regulatory approaches. Some examples are:

- Regulatory decisions based on risk management
- Improvements in the production process, within the approved design area, without further regulatory review.
- Reduction of submissions after approval.
- Real-time quality control, thus reducing the final product release test

The main body of Directive ICH Q8 describes the knowledge acquired and must be described in relation to the development of the medicinal product, for each of its components and the manufacturing process.

Initially, in relation to the active substance, its physicochemical and biological characteristics that can affect the yield of the final product and the production process must be identified and described. Examples of these characteristics are solubility, particle size, water content, etc. Also, compatibility with excipients or other active substances should be investigated if they are contained in the final product.

Regarding the excipients, the choice of excipients, their concentration and physicochemical characteristics that affect the performance of the final product must be studied. This refers to the substances used in the production of the final product whether they appear in the final product or not (e.g., processing aids). As with the active substance, compatibility with the other excipients of the composition should be investigated. In addition, the ability of the excipient to provide its intended function throughout the shelf-life of the product must be demonstrated and, finally, information on the safety of excipients must be provided.

Furthermore, during the development of the medicinal product, the steps taken at the stage of pre-formulation should be described and the CQAs that affect the quality of the final product should be mentioned, considering the intended use and the route of administration. CQAs can be identified using experimental design. In addition, both the choice of ingredients and packaging and the limits chosen for them during development, the production process and the potential knowledge gained from the development of similar products must be emphasized and justified. A summary of the in vitro or in vivo studies performed and their correlation with the proposed production process as well as in vitro / in vivo correlations that may help reduce bioavailability studies should also be provided. Additionally, if there are any specific characteristics in the product or in its design their existence must be mentioned and justified. Finally, all physicochemical and biological characteristics related to the safety, performance or manufacturing capability of the product must be reported and analyzed. This includes controls that have been selected or developed to determine the above characteristics.

Directive ICH Q8 also includes the development of appropriate production processes. The selection, the control but also any improvements in the production process must be justified. The critical attributes of the formulation in relation to the available process options must be taken into account to justify the suitability of the process and equipment. The development studies of the appropriate production processes are the basis for process improvement, process validation, continuous process verification and any process control

requirements. Also, at this stage the CPPs that affect the quality of the final product must be identified, monitored, and controlled to ensure that the final product has the desired quality.

In addition, significant differences between the pilot-scale and commercial-scale production process that affect process efficiency, quality and manufacturing capacity of the final product must be reported. When developing production processes, in order to provide flexibility for future process improvement, it is useful to describe the systems for monitoring and recording CPPs. This can enable the collection of information in order to gain further knowledge and understanding of the process. Understanding the robustness of the process combined with quality risk management (QRM) can support future improvement of the production process. Finally, both process control strategies that offer adjustment of critical parameters and the assessment of process capability to ensure the desired quality of the final product must be described.

The next part analyzed in Directive ICH Q8 is the development and use of appropriate packaging. The choice of the type of packaging depending on the intended use of the product and the suitability of the packaging during both storage and transport must be justified. Also, the choice of packaging material in relation to the integrity of the container, the possible interactions of the product with the packaging or label as well as the ability of the material to protect the product from moisture or light and safety materials must be considered and justified. Finally, if a dosing device (e.g., dry powder inhaler) is used, it is very important to demonstrate dose accuracy and repeatability when using the device.

It is obvious that the directive focuses and demands deep knowledge and understanding in all stages of development. Only through experimental design and especially QbD this can be achieved, and all the knowledge can be acquired and reported through solid scientific data.

I.2.4.1.1. Quality by Design (QbD)

The ICH Q8 Directive contains in its annex the essence of the development of pharmaceutical forms, as it analyzes the key methods used and offer the maximum knowledge at this stage, which is the QbD approach. In the main body of the directive, two approaches to the development of pharmaceutical forms are mentioned, the basic or empirical approach and the systematic approach or QbD.

In the empirical approach, the choices of the key product features and process parameters are made empirically, thus wasting time, effort, and cost in investigating the optimal variables, which in reality may not even be the best or lead to the right conclusions, as questions remain unanswered. On the contrary, using the systematic approach to development, the results are more reliable, knowledge of both the product and the process is provided throughout the shelf- life of the product, this knowledge is based on scientific principles and helps to achieve the desired quality. Finally, it helps with more flexible regulatory approaches (International Council for Harmonisation Q8, 2009).

The development of pharmaceutical forms must contain at least the following:

- The ideal quality characteristics of the product, the Quality Target Product Profile (QTPP), which are associated with quality, safety and efficiency. To define these, for example, the route of administration, stability, dose, form, bioavailability, etc. must be considered.
- Then the potential critical quality characteristics of the product, the Critical Quality Attributes (CQAs) are investigated and defined. What ultimately affects the quality of the final product must be studied and controlled.

- The critical quality characteristics for the product ingredients, the Critical Material Attributes (CMAs), such as the active ingredient and the excipients, are then defined and the appropriate quantities are selected that will impart the desired quality to the product.
- The appropriate production process is selected.
- The control strategy is defined.

Using the enhanced approach to the development of pharmaceutical forms, in addition to those mentioned, it also includes:

- Systematic evaluation, understanding and improvement of the composition and production process. This includes:
    - Determining properties of materials and process parameters that affect critical product quality characteristics (CQAs) through prior knowledge, experimentation and quality risk management.
    - Determining the relationships between material properties and process parameters and critical product quality characteristics (CQAs).
    - In combination with the quality risk management strategy, an appropriate control strategy can be established (e.g., it may include a proposal for site design, real-time release tests).

All this results in a more systematic approach that can help continuously improve and innovate throughout the shelf-life of the product.

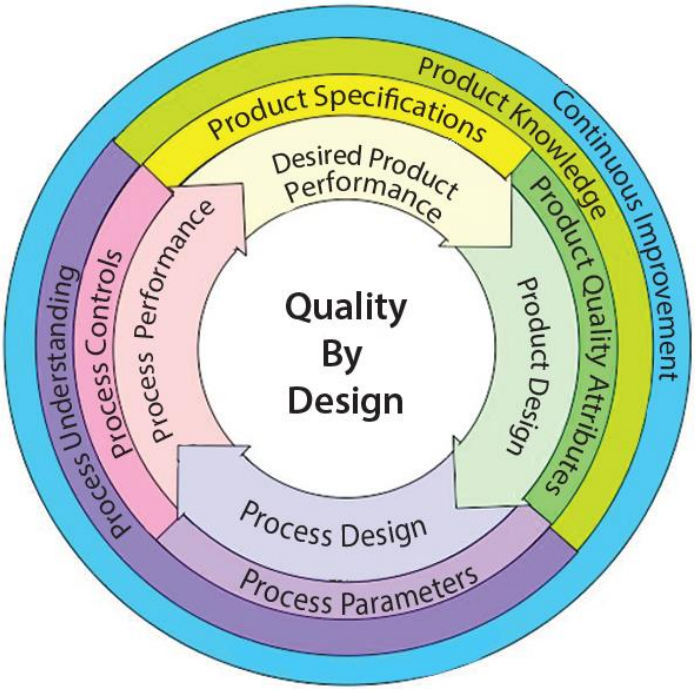


Figure I.2.16: The aspects of QbD (Torres, 2015).

As shown in the figure, QbD encloses and is enclosed by the knowledge and understanding of the product and the production process, the desired performance and quality is achieved while at the same time offering opportunities for continuous improvement.

Table I.2.4: Comparison of empirical and enhanced approaches to pharmaceutical development (International Council for Harmonisation Q8, 2009).

Aspect	Minimal Approaches	Enhanced, QbD Approaches
Overall Pharmaceutical Development	• Mainly empirical • Developmental research often conducted one variable at a time	• Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • Establishment of design space • PAT tools utilized
Manufacturing Process	• Fixed • Validation primarily based on initial full-scale batches •Focus on optimization and reproducibility	• Adjustable within design space • Lifecycle approach to validation and, ideally, continuous process verification • Focus on control strategy and robustness • Use of statistical process control methods
Process Controls	• In-process tests primarily for go/no go decisions • Off-line analysis	• PAT tools utilized with appropriate feed forward and feedback controls • Process operations tracked and trended to support continual improvement efforts post-approval
Product Specifications	• Primary means of control • Based on batch data available at time of registration	• Part of the overall quality control strategy • Based on desired product performance with relevant supportive data
Control Strategy	• Drug product quality controlled primarily by intermediates (in-process materials) and end product testing	• Drug product quality ensured by risk-based control strategy for well understood product and process • Quality controls shifted upstream, with the possibility of real-time release testing or reduced end-product testing.
Lifecycle Management	• Reactive (i.e., problem solving and corrective action)	• Preventive action • Continual improvement facilitated

QbD Steps

Figure I.2.17: The QbD steps (Torres, 2015).

The first step of QbD is to identify the needs of the patient, to define the product we want to produce to meet those needs and to see how they relate to the product. This is how we define the QTPP, the ideal quality characteristics of the product. Examples of QTPP are dosage, route of administration, uniformity of content, packaging, characteristics affecting the release of the active substance such as solubility, hardness, stability, etc.

The next step is to recognize the CQAs. These characteristics can be physicochemical, biological, microbiological and must be within certain limits, a range, or a distribution, not to affect the quality of the final product. For example, for a solid formulation, CQAs may be parameters that affect purity, strength, release, and stability. For inhaled products, it may be the aerodynamic properties of the particles, for parenteral administrations it may be sterility, while for transdermal formulations, the adhesion properties.

The potential CQAs are recognized as critical based on QTPP and prior knowledge e.g., the development of a similar product. The list of CQAs does not remain untouched but may change as product and process development continues and further knowledge is acquired. Also, Quality Risk Management (QRM) can help categorize and prioritize potential CQAs and in combination with some experiments it can be recognized that their variability can affect product quality.

The third step is risk assessment. Risk assessment is part of the ICH Q9 Directive and is a valuable science-based tool that can help identify the Critical Material Attributes (CMAs) and CPPs that potentially affect the CQAs. Essentially Risk assessment links CMAs and CPPs to product CQAs. Typically, the risk assessment is performed early in the process of developing pharmaceutical forms and is repeated as more information is available and more knowledge is gained. It is used to categorize the characteristics based on prior knowledge and initial experimental data. Risk management and especially risk assessment are analyzed in next sections.

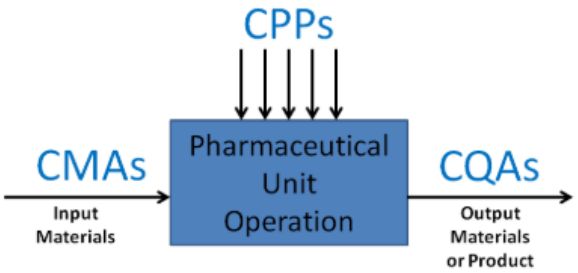
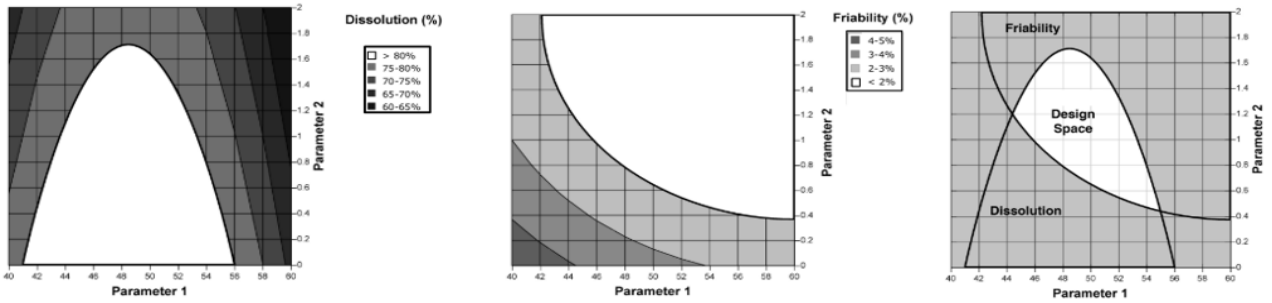


Figure I.2.18: The connection between CPPs, CMAs and CQAs (U.S. Food and Drug Administration (FDA), 2012).

Once the parameters of the materials and process and the characteristics of the product that are affected are identified, the next step is to find the relationship that these are associated with. The risk assessment performed in conjunction with some experiments can lead to an understanding of the link between CMAs,

CPPs and CQAs as well as the identification of variables and the limits within which they can move without affecting product quality. These limits are described by Design Space. The choice or deviation of variables from the design space and how they affect quality must be described and justified. Subsequently, the design space must be described. This can be done in a number of ways, such as the range of values that CMAs and CPPs can vary, or with some mathematical models. It is also possible for the design space to be described as a function of time, temperature, etc. or with a combination of variables. Scaling factors can be included in the design space especially if the design space is going to cover multiple operating levels. Finally, analysis of historical data can help to create the design space. Regardless of how the design space is described, it is expected that working within its boundaries will result in a product with the desired quality characteristics.

For example, as depicted in Figure I.2.19 the design space has been selected to be described by the common operating range of several CQAs. That is, suppose that two parameters of the granulation process are studied which affect the dissolution rate and the friability of the produced tablet. The first diagram shows the dissolution rate as a function of parameters 1 and 2 and the second diagram shows the friability as a function of the same factors. By combining the two curves, the limits of parameters 1 and 2 can be found for the optimal development of the process, thus defining the design space (International Council for Harmonisation Q8, 2009).



Contour plot of dissolution as a function of parameters 1 and 2.

Contour plot of friability as a function of parameters 1 and 2.

Proposed design space, comprised of the overlap region of ranges for friability and or dissolution

Figure I.2.19: Example 1 of the description of design space (International Council for Harmonisation Q8, 2009).

In a second example, having the dissolution rate as a criterion, one can choose to define the design space with a mathematical model of the two parameters either non-linear but with a larger range of values, or with a linear model and a smaller range of values but more functional (International Council for Harmonisation Q8, 2009).

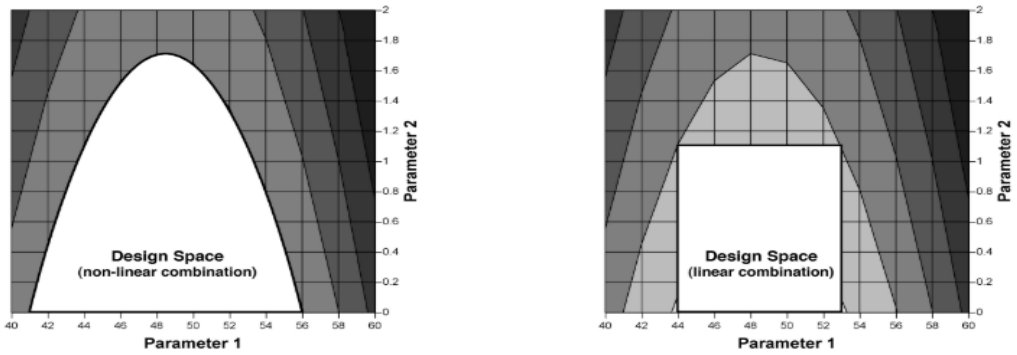


Figure I.2. 20: Example 2 of the description of design space (International Council for Harmonisation Q8, 2009).

Different design spaces can also be defined for each unit operation separately or a single design space. In the first case it is easier to define it, but in the second case it offers more flexibility. Also, the design space can be developed for any production scale, whether it is pilot or commercial. However, it must be justified that the pilot scale is linked to the commercial scale and the potential risks during the scale up process should be emphasized. If the design space is proposed to be used on multiple scales, then the design space must be described by parameters that are not affected by the production scale.

The next step of QbD is the control strategy. The control strategy is designed to ensure a production of goods of the required quality continuously and consistently. The control strategy describes the controls during the process or the controls of the raw materials, intermediates, packaging, or final product and how they are performed so that the final product has the desired quality. They must be based on an understanding of the product, the composition and the process and must include at least the control of the CPPs and the CMAs.

Using an enhanced pharmaceutical development approach, a greater understanding of the product and the process is achieved so that the sources of variability can be properly identified and controlled. Recognizing the sources of variability and their impact on subsequent processes, materials and quality of medicinal products can provide the opportunity to shift controls earlier in the process, minimize the need for final product controls and use alternative methods to ensure quality of materials and therefore real-time release testing can be performed. For example, disintegration could serve as a substitute for the dissolution rate in the case of solid forms of rapid disintegration containing highly soluble active substances. Also, if content uniformity is done in-process (e.g., with weight variation and NIR) it could allow real time release testing and offer an increased level of quality assurance compared to traditional end product testing using content uniformity standards.

The control strategy may include (International Council for Harmonisation Q8, 2009):

- Controlling the input CMAs (e.g., active substance, excipients, packaging materials) based on an understanding of their impact on product quality
- Product specifications
- Controls for unit operations that have an impact on subsequent processing or product quality
- In-process control or real-time release testing
- A monitoring program for verifying multivariate prediction models.

The control strategy may combine different controls, for example a control based on testing the final product and a control based on real-time testing.

The last part of QbD refers to the continuous improvement of product quality and production process. As analyzed in ICH Q10 Directive, the product quality over its life cycle can be improved by manufacturers by evaluating innovative approaches. This can be done by monitoring the performance of the process and ensuring that it works as expected. This monitoring may include trend analysis of the production process if more knowledge and experience is gained while production is ongoing. For processes where the design space is described by mathematical models, periodic maintenance can be performed to evaluate and ensure the performance of the model. Also, as additional knowledge of the process is gained, the design space can be expanded, reduced, or even redefined. Of course, the change of design space is subject to regional requirements.

Overall, the enhanced approach to the development of pharmaceutical forms or Quality by Design, can expand the knowledge about the product and the production process. It is based on scientific data and helps in making the right decisions. Enhances monitoring, control and product and process development. It facilitates continuous improvement and innovation as well as saving costs and increasing efficiency. With QbD, fewer checks can be performed, and products can be released in real time. Finally, the use of QbD facilitates regulators and their requirements.

I.2.4.2. ICH Q9 – Quality Risk Management (QRM)

This directive provides guidance on the principles and some of the risk quality management tools that can enable more effective and consistent risk-based decisions about the quality of pharmaceutical drugs and products throughout the product life cycle. These aspects can be applied from development and manufacturing to distribution, packaging, raw materials, or submission (International Council for Harmonisation Q9, 2005). The Directive ICH Q9 is closely connected to the Directive ICH Q8. As mentioned to earlier section, the third step of the QbD was the risk assessment to identify the CMAs and CPPs that potentially affect the CQAs of the product. This directive refers to the tools that can be used to evaluate the CMAs and CPPs and to categorize the risk that each potentially poses to the quality of the final product.

The directive begins by defining risk as the combination of the probability of occurrence of harm and the severity of that harm (harm & severity). In pharmacy, this risk always concerns the patient, and its management is of primary importance.

This directive describes a systematic approach to evaluating, controlling, communicating, and reviewing the risks to a product's quality throughout its life cycle. It complements other guidelines and offers tools for more effective and consistent decision making. The directive has two basic principles:

- QRM should be based on scientific knowledge and ultimately linked to patient protection.
- The level of effort, formulation, and documentation of the QRM process must be proportional to the level of risk.

Figure I.2.21 depicts the three basic processes of QRM:

- Risk assessment
- Risk control
- Risk review

Each process follows the completion of the previous process and simultaneously are linked through the process of risk communication. Enablers of the QRM process are the Risk Management Tools. In the following pages, each individual step of QRM is analyzed in detail.

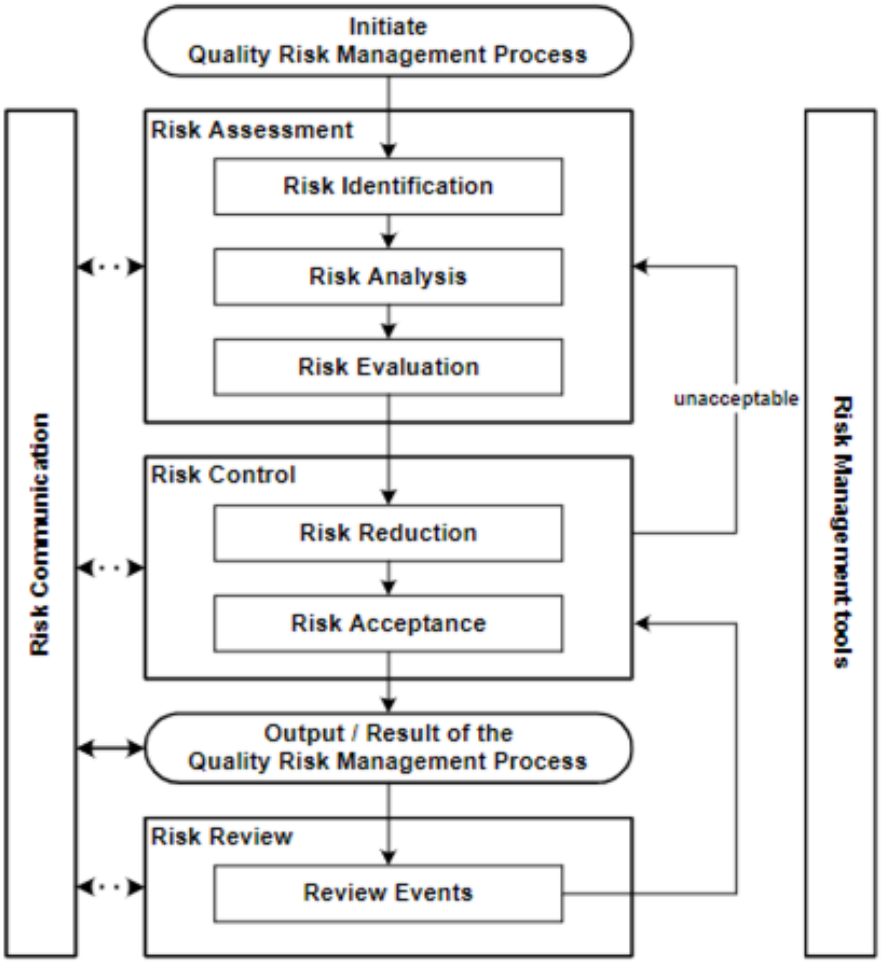


Figure I.2.21: Quality Risk Management (International Council for Harmonisation Q9, 2005).

Risk assessment is used for the identification of risks and the analysis-assessment of the risks associated with exposure to these risks. The following questions are answered in this section:

What might go wrong? So, what is the risk?

What is the probability that it will go wrong?

What are the consequences if it goes wrong? So, the severity.

Part of risk assessment is Risk Identification, in which a systematic use of information identifies potential hazards, thus answering the first question what might go wrong, including the possible consequences. Input information can be historical data, theoretical analysis, or informed opinions.

Subsequently, Risk Analysis is performed in order to estimate the risk associated with the identified hazards. At this step, the second and question are answered, providing a qualitative or quantitative estimation, linking the probability of occurrence and the severity of harms. Also, the detectability can be included in this section, providing additional estimation of the risk based on the ability of the system to detect the harm.

Finally, Risk Evaluation is performed in order to compare the identified and analyzed risk against given risk criteria. All data provided in the previous steps are analyzed based on their quality and robustness. Assumptions and reasonable sources of uncertainty are revealed, and the limitations of the system are identified strengthening the output of risk assessment. Incomplete knowledge or unexpected variability are sources of variability.

After the completion of risk assessment, a qualitative or quantitative output is provided, ranking the risk either by a numeric score or as "high", "medium", or "low". This score is calculated by risk management tools based on the probability, severity and maybe detectability.

At this point, the CQAs and CPPs that affect the CQAs of the product are essentially identified, evaluated, and categorized. This is the connection with the ICH Q8 Directive and the development of pharmaceutical forms.

Risk control is the next step of QRM, which is essentially the control strategy. At this point it is recognized if the risk exceeds the acceptable limits. If this is the case, the appropriate control strategy is in place to reduce or eliminate the risk, always in relation to the probability and consequences of the risk. The amount of effort used to control the risk should be proportional to the significance of the risk. If the risk is controlled, it must be determined whether new risks are introduced as a result of the identified risks control. This part of risk control is the Risk Reduction step.

In the cases in which the risk cannot be reduced below an acceptable threshold or eliminated even after an appropriate control strategy is in place, the existence of the risk is accepted. This part of risk control is the Risk Acceptance step in which a formal decision is taken to accept the residual risk, or a passive decision is taken in which residual risks are not specified and cannot be entirely eliminated.

Risk control might focus on the following questions:

Is the risk above an acceptable level?

What can be done to reduce or eliminate risks?

What is the appropriate balance among benefits, risks and resources?

Are new risks introduced as a result of the identified risks being controlled?

Risk Review is the last key step of the methodology, which aims at continuous improvement. Each time the methodology is implemented, its results must be reviewed to take into account new knowledge and experiences.

Risk Communication is a parallel part of QRM that involves all parties of the system and includes the sharing of information about risk and risk management. Parties can communicate at any stage of the risk management process. The output/result of the QRM process should be appropriately communicated and documented.

The QRM Tools are the enablers of the QRM methodology used to assess and manage risk. Traditionally, empirical, or internal procedures based on trends and/or observations have been used as sources of information for QRM. Nowadays, this methodology in combination with universally accepted QRM tools can provide a scientific and practical approach to decision making as it provides documented, transparent, and reproducible methods based on the assessment of probability, severity, and detectability. Examples of these QRM tools are (International Council for Harmonisation Q9, 2005):

- Basic risk management facilitation methods
  - Flowcharts
  - check sheets
  - Cause & Effect Diagram etc.
- Main Risk Management Techniques
  - Failure Mode Effects Analysis (FMEA)
  - Failure Mode, Effects and Criticality Analysis (FMECA)
  - Fault Tree Analysis (FTA)
  - Hazard Analysis and Critical Control Points (HACCP)
  - Hazard Operability Analysis (HAZOP)
  - Preliminary Hazard Analysis (PHA)
  - Risk ranking and filtering
- Supporting statistical tools
  - Control Charts
  - Design of Experiments (DoE)
  - Process Capability Analysis (PCA)
  - Statistical Process Control (SPC)
  - Pareto Charts
  - Histograms etc.

One of the most widely used tools is Failure Mode Effects Analysis (FMEA) as it is based on the understanding and knowledge of the process, it is a flexible method and divides complex processes into manageable steps.

This tool is used to identify possible failures, examine changes in product quality and suggest appropriate corrective and preventive actions. For the qualitative and quantitative assessment of the risk, a variable called Risk Prioritization Number (RPN) is used and it is calculated by multiplying the probability of a failure, the severity, and the detectability of the risk. This multiplication gives us a numerical score for each step of the process that something can go wrong and in this way the risk can be categorized (WHO, 2013).

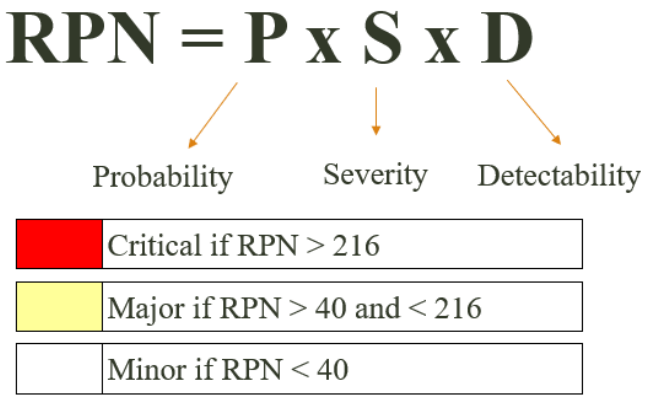


Figure I.2.22: Risk Prioritization Number (WHO, 2013).

If the RPN variable is greater than 216 then the risk is considered critical and must be addressed immediately. The root cause must also be investigated, and corrective and preventive actions taken.

If the RPN variable is between 40-216 then the risk is classified as major and must be addressed in a timely manner. In this case, too, the root cause must be investigated, and corrective and preventive actions taken.

Finally, If the RPN variable is less than 40 the risk is classified as low and must be addressed. Although these types of hazards generally do not affect batch release, they should be addressed prior to release. If necessary, in this case as well, the root cause can be investigated, and the appropriate corrective and preventive actions must be taken.

To calculate RPN the probability, severity and detectability of the risk must be categorized and quantified in some way. According to the WHO directive (WHO, 2013) this can be done according to the following table.

Table I.2.5: Categorization of probability, severity and detectability of the risk for the Risk Prioritization Number (RPN) calculation (WHO, 2013).

Probability	**P (*)**	**Description**
Extremely Low	2	Highly improbable to occur
Low	4	Improbable to occur
Moderate	6	Probable to occur
High	8	Highly probable to occur
Severity	**S (*)**	**Description**
Low	2	Minor GMP non-compliance; no possible impact on patient, yield or no production capability
Moderate	4	Significant GMP non-compliance; possible impact on patient; moderate impact on yield or production capability
High	6	Major GMP non-compliance; probable impact on patient; high impact on yield or production capability
Critical	54	Serious GMP non-compliance; Probable serious harm or death; impact on yield or production capability
Detectability	**D (*)**	**Description**
High	2	Control System in place has a high probability of detecting the defect or its effects
Moderate	4	Control System in place could detect the defect or its effects
Low	6	Control System in place has a low probability of detecting the defect or its effects
Non-existent	8	There is no control system to detect the defect

For example, when the risk is too unlikely to happen, the probability gets the value 2, while when it is too high, it gets the value 8. The same happens with the severity, when the severity of the risk is low it is given the value two, while when severity is high, it gets the value of 54. In reverse, when the detectability is high it gets the value of two, while when detectability is low or there is no control, the value of the variable is high.

In the same Directive, Deviation Handling and Quality Risk Management (WHO, 2013), WHO proposes a decision-making process for managing deviations. This process consists of a sequence of five steps.

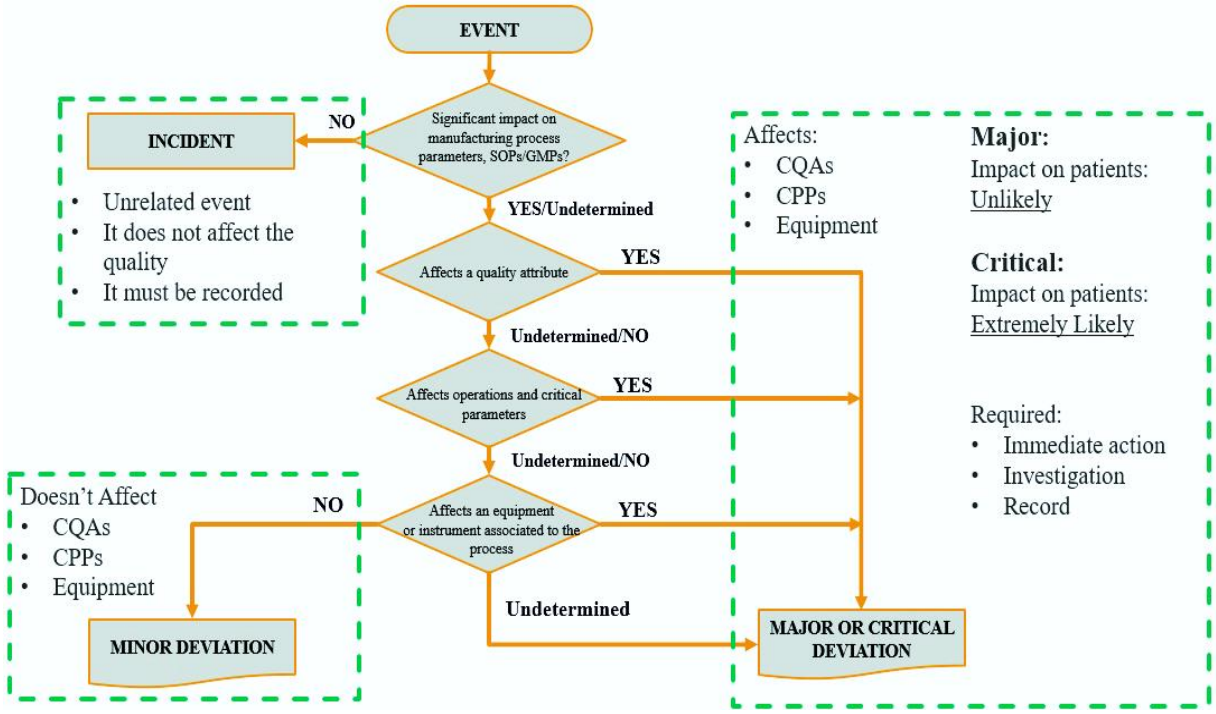


Figure I.2.23: Decision Tree for Deviation Classification (WHO, 2013).

The first step is to detect the events. The way the staff reacts when a deviation is observed is the first challenge in handling deviations and depends on the level of training, qualifications, commitment, and support of the senior management. A key requirement for handling deviations is for staff to be vigilant, to be able to identify potential adverse events, and to know clearly what to do about recording and communicating them. Techniques such as the decision tree can be used to systematize and improve staff response and decision-making, which helps identify differences based on risk and their effects on quality and then classification, recording and their research.

The second step is to categorize deviations (the decision-making process). This is done with the use of a decision tree, which is essentially a simplified risk assessment. Whenever there is a deviation, the decision tree helps answer two questions: Does the event affect a property of the product, a construction parameter, or the quality of the product? and Does the event contradict or omit a requirement or directive which is included in any approved procedure or specification?

If the answer to the above questions is NO, then the incident is classified as an INCIDENT, which is a non-relevant event that does not affect the quality. However, it should be recorded in case it happens again or in case it is connected to another event. If even one answer to the above questions is NO, then there is a procedure for classifying the event, in minor, major or critical, which must be based on the impact and risk of the process and the quality of the product through the use of any QRM tool. When the deviation does not affect any CQAs, CPPs or any equipment of the production process, then the deviation is classified as Minor and must be treated appropriately. When the deviation affects any of the CQAs, CPPs or the equipment of the production process, but the effects on the patients are unlikely, then the deviation is characterized as Major and requires immediate action, investigation and recording by the appropriate SOP. Finally, when the deviation affects any of the CQAs, CPPs or the equipment of the production process and

the effects on the patients are extremely probable, then the deviation is characterized as Critical and requires immediate action, investigation and recording by the appropriate SOP (WHO, 2013).

The third step in handling deviations is Deviation Treatment, i.e., how the deviations will be treated.

If a deviation is marked as Minor, then the steps followed are:

- The description of the deviation, i.e., the data proving the deviation, the time when it took place, the place and the person who recognized the deviation.
- The correction of the deviation, i.e., the measures taken. These corrective actions must first be approved by the QA or if this is not possible, a responsible staff member can approve the corrective actions, which must then be approved by the QA as soon as possible.
- Then, the effectiveness of the corrective actions is validated and recorded.
- Finally, all information is recorded in a database for traceability purposes.

Table I.2.6: Minor Deviation Treatment (WHO, 2013).

Item #	MINOR DEVIATION
1	Description
2	Correction
3	Efficacy and Conclusion
4	Data base record

In the case of major or critical deviations a more enhanced approach is required.

- A more detailed and thorough description of the deviation is initially recorded, which helps to investigate the causes.
- Corrective actions are then carried out which, as in the case of minor deviations, must have been approved by the QA and the underlying cause is investigated.
- Once the root cause has been found, corrective and preventive actions are applied, while their effectiveness is evaluated.
- Finally, all the information is recorded in a database.

Table I.2.7: Major or Critical Deviation Treatment (WHO, 2013)

Item #	Major or Critical Deviation
1	Description
2	Correction
3	Efficacy and Conclusion
4	Batch Disposition if applicable
5	Root Cause Investigation
6	Corrective-Preventive Actions (CAPA)
7	Efficacy of Corrective Actions
8	Conclusion
9	Data base record

The fourth step in handling deviations is to investigate the root causes. As mentioned, this is required in case the deviation is characterized as major or critical, but it is also useful in the case of minor deviations

as it is a useful tool for quality improvement. The most popular and simple tool for investigating the root causes is the 5M + E or Ishikawa, fishbone diagram. This diagram shows the process or product as the backbone, while the branches are the possible causes of the deviation / effect.

The final step in handling deviations is Corrective and Preventive Actions or CAPAs and are used to eliminate root cause deviations. This will be analyzed in more detail in later sections, in the ICH Q10 directive as it is a key tool for Continuous Improvement of Process Performance & Product Quality.

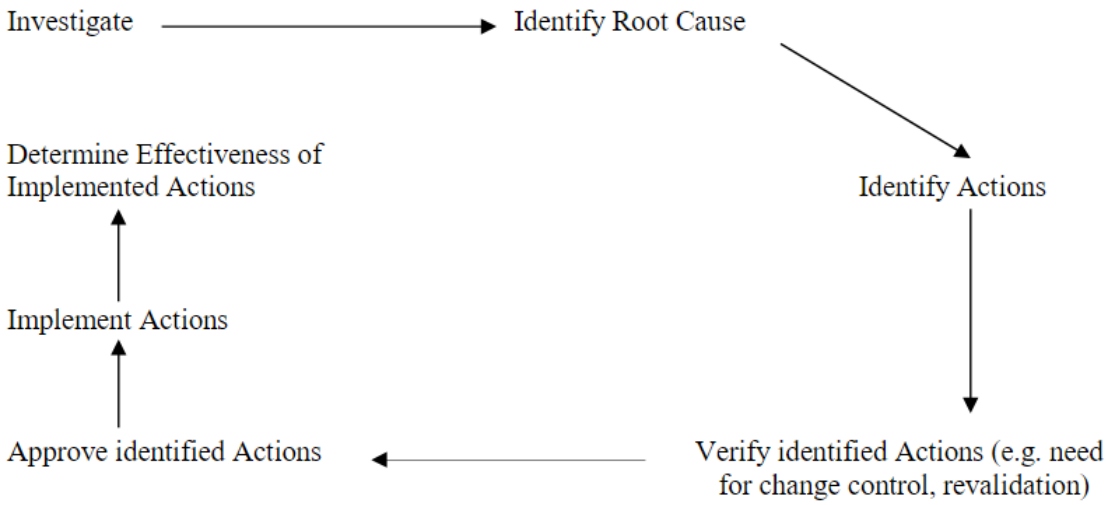


Figure I.2.24: CAPA strategy – Improvement Process (WHO, 2013)

I.2.4.3. ICH Q10 – Pharmaceutical Quality System (PQS)

Directive ICH Q10 describes one comprehensive model for an effective pharmaceutical quality system (PQS) that incorporates all quality regulations such as International Standards Organization (ISO) quality concepts, Good Manufacturing Practice (GMP) regulations and components ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management". ICH Q10 can be implemented throughout the different stages of a product lifecycle (International Council for Harmonisation, 2008).

Figure I.2.25 illustrates the key features of the PQS - ICH Q10. PQS covers the entire life cycle of a product, including pharmaceutical development, technology transfer, commercial production, and product discontinuation. PQS complements, increases, magnifies GMPs as shown in the figure. The next horizontal bar illustrates the importance of management responsibilities at all stages of the product life cycle, while the PQS elements demonstrated in the following horizontal bar are the main pillars in the PQS model. These include process performance and product quality monitoring system, CAPA system, change management system and management review. These elements must be applied appropriately and proportionately at each stage of the life cycle, recognizing opportunities for continuous improvement. Finally, the last set of horizontal bars depicts the driving forces of the model: knowledge management and quality risk management, which apply throughout the life cycle. These driving forces are not other than what has been described so far, the ICH Q8 and Q9 directives. These mechanisms support the goals of PQS, to achieve product implementation, create and maintain a control status as well as continuous improvement.

Figure I.2.25: Pharmaceutical Quality System ICH Q10 (International Council for Harmonisation Q10, 2008).

The implementation of the Q10 model should lead to the achievement of three main objectives that complement or reinforce the regional requirements of good practice. The first goal is product realization, i.e., the establishment, implementation and maintenance of a system that allows the delivery of products with quality characteristics that meet the needs of patients, health professionals and authorities. The second goal is to achieve the state of control. Through the development and implementation of systems for monitoring and controlling the performance of the process and the quality of the product, it is possible to ensure both the suitability and the capacity of the process. QRM can help for choosing the right monitoring and control system. The third goal of Q10 is Continuous Improvement. This can be done by identifying and implementing appropriate improvements for better product quality, production process, reducing variability or even applying quality system innovations. These implementations increase the ability to meet the quality needs consistently.

Product life cycle

The first part of the directive refers to the product life cycle, which includes the following technical activities: Pharmaceutical development, technology transfer, Commercial Manufacture and Product Discontinuation. Pharmaceutical development includes the processes from the development of the active substance and the pharmaceutical form to the production process and the analytical methods. The technology transfer activity refers to the transfer of knowledge, both from the development phase to the production phase for the new products and within or between the production and testing areas for the products that are commercially available. In commercial manufacturing activities such as control of materials, facilities and equipment, quality control and assurance up to storage and distribution are included. Finally, the life cycle of a product also includes the discontinuation of the product from the market. This

stage includes activities such as the preservation of documents and samples as well as the continuation of product evaluation and reporting.

The ICH Q7 Directive 'Good Manufacturing Practice, Guide for Active Pharmaceutical Ingredients', GMP and ISO quality management system are the foundations of Q10 Directive. To achieve the objectives of the directive, namely product realization, state of control and continuous improvement, Q10 complements and reinforces GMPs by describing specific quality system elements and management responsibilities. It provides a harmonized model for a QPS throughout the life cycle of a product and is intended to be used in conjunction with GMPs. Finally, since GMPs do not cover all stages of the product life cycle, such as pharmaceutical development, ICH Q10 aims to encourage the use of science and risk management approaches at every stage of the life cycle, thus promoting continuous improvement throughout the product life cycle. Regarding the link between Q10 and regulatory approaches, it is stated that regulatory approaches to a particular product or process should be analogous to the level of understanding of the product and process, the results of quality risk management and the effectiveness of the PQS.

The two driving forces that enable the implementation of ICH Q10 effectively and successfully are the knowledge management and quality risk management i.e., ICH Q8 and Q9 Directives. The first part concerns the management knowledge derived from product and production process acquired from the development stage to the marketing and discontinuation of the product from the market. Knowledge management is a systematic approach to obtaining, analyzing, storing, and spread of information related to the product, the production process, and the equipment. As mentioned, sources of knowledge are the process of developing pharmaceutical forms, prior knowledge, improvement processes, experience, etc. that is contained in Directive Q8. The second driving force is QRM, which is an integral part of an effective PQS. It can offer an approach to identifying, scientifically evaluating, and controlling potential quality hazards. It facilitates the continuous improvement of process efficiency and product quality throughout the product life cycle. ICH Q9 provides principles and examples of quality risk management tools that can be applied to different aspects of pharmaceutical quality.

Management Responsibilities

Deming was the first to emphasize management responsibility as the starting point for improving quality and productivity. This is also reflected in Directive ICH Q10, which considers management to be essential to creating and maintaining a commitment to the quality and performance of the PQS throughout the organization. ICH Q10 divides the responsibilities of management into eight sub-sections which concern:

- Management Commitment
- Quality Policy
- Quality Planning
- Resource Management
- Internal Communication
- Management Review
- Management of Outsourced Activities and Purchased Materials
- Management of Change in Product Ownership

All of these individual guidelines describe in detail what the administration needs to do in order to implement an effective PQS.

The responsibility of management is emphasized in all the directives regarding the quality of the product and the process. It is worth mentioning the directive issued in 2006 by the FDA, 'Guidance for Industry - Quality Systems Approach to Pharmaceutical CGMP Regulations', which in the last part of the conclusions mentions the support of the administration both philosophically and financially. This emphasizes the loyalty and commitment that management must have in all areas and activities of the organization in order to produce consistently, safe, and effective pharmaceutical products (US Food and Drug Administration, 2006).

Continuous Improvement of process efficiency and product quality

The last part of Directive Q10 describes the ways in which continuous improvement of process efficiency and product quality can be achieved. It starts with the product life cycle activities and goals that increase GMP regional requirements. As far as pharmaceutical development is concerned, the goal is to design a product and a production process in order to consistently achieve the desired performance and to meet the needs of patients and health professionals, regulators, and internal customer requirements. Thus, the acquisition of knowledge. All of these are described in ICH Q8 Directive. For technology transfer, the goal is to transfer this knowledge between development and manufacturing and within or between production sites to achieve product realization. This knowledge is the basis for the production process, the control strategy, process validation and continuous improvement.

The goals of commercial manufacturing include achieving product realization, creating, and maintaining a state of control and facilitating continuous improvement. Also, a PQS should ensure that the desired quality of the product is systematically satisfied, the proper performance of the process is achieved, that all controls are appropriate, that opportunities for improvement are identified and evaluated and finally, that knowledge is constantly expanding. Furthermore, the goal of product discontinuation is an effective management of the terminal stage of the product life cycle, a predetermined approach to managing activities such as document and sample retention or ongoing product evaluation and suitable reporting complying with regulatory requirements.

The pillars of the quality pharmaceutical system through which continuous improvement of performance and quality can be achieved are:

- Process Performance and Product Quality Monitoring System
- Corrective and Preventive Action System (CAPA)
- Change management system
- Management review of process performance and product quality

In more detail, a process performance and product quality monitoring system should be designed and implemented to ensure that a state of control is maintained. An effective monitoring system ensures the continuous capability of the processes and controls to produce a product of the desired quality and identifies areas for continuous improvement. The monitoring system should use quality risk management to define the control strategy. This may include parameters of materials, process, equipment and facilities, final product and related methods, and frequency of monitoring and control. The control strategy should facilitate timely feedback (feed / feedforward) and appropriate corrective and preventive actions. It must also provide the tools for measuring and analyzing the parameters and characteristics identified in the control strategy. It should also analyze the parameters and characteristics identified to verify continuous operation in control mode, identify sources of variability that affect process performance and product quality for possible

ongoing improvement activities to reduce or control variability. Moreover, it should include product quality feedback from both internal and external sources, e.g., from complaints, product rejections, non-compliances, reminders, deviations, controls and inspections and findings of regulatory authorities. Finally, the monitoring system should provide knowledge to enhance understanding of the process, to enrich the design space, and to activate innovative approaches to process validation.

Table I.2.8: Application of Process Performance and Product Quality Monitoring System throughout the Product Lifecycle (International Council for Harmonisation Q10, 2008).

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Process and product knowledge generated, and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.

The second pillar of Q10 is the Corrective and Preventive Action System (CAPA). Every pharmaceutical company must have and implement a CAPA system, which is the result of the investigation of complaints, product rejections, non-compliances, recalls, deviations, controls, inspections, and findings of regulators, as well as trends in its performance, process, and product quality monitoring. The CAPA system is a structured approach to investigation that aims to determine the root cause. The level of effort, wording and documentation of the research should be analogous to the level of risk, according to ICH Q9. The CAPA methodology should result in both improved and increased understanding of products and processes.

Table I.2 9: Application of Corrective Action and Preventive Action System throughout the Product Lifecycle (International Council for Harmonisation Q10, 2008).

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Product or process variability is explored. CAPA methodology is useful where corrective actions and preventive actions are incorporated into the iterative design and development processes.	CAPA can be used as an effective system for feedback, feedforward, and continual improvement.	CAPA should be used, and the effectiveness of the actions should be evaluated.	CAPA should continue after the product is discontinued. The impact on product remaining on the market should be considered as well as other products which might be impacted.

WHO Directive, 'Deviation Handling and Quality Risk Management' (WHO, 2013), mentions the management of deviations and the methodology that is followed. The steps for handling deviations are:

- Event Detection

- Deviation Categorization / Decision Making process
- Deviation Treatment
- Root cause Investigation
- Corrective and Preventive Actions (CAPA)

Corrective actions are taken to eliminate the root cause of the deviations and must be based on quality research. Prior to their application, their effectiveness must be approved by the QA in a documented manner, which requires a significant period of time. Therefore, corrective actions can be transferred to an independent CAPA system to avoid unnecessary delays. This standalone CAPA system should include a detectability method for all actions and performance, as required by a predefined CAPA plan. Corrective are activated in response to detectable deviations and can cause preventive actions. However, not all corrective actions are related preventive actions. Preventive actions are initially associated with non-compliances and act on similar processes, production lines or different places where there is no deviation yet but there is a possibility in the future. To achieve this, the QRM must identify the different sources of information to be followed and evolve as part of a systematic, periodic, and documented evaluation, which is usually directed by the QA. Possible strategies and tools to be used for this purpose are described in ICH Q9 (WHO, 2013).

As part of the CAPA and improvement process, activities such as product and quality system review (e.g., Annual Product Review) provide an opportunity to summarize aggregated information as well as findings and trends on an annual basis in order to identify a systematic action to improve the quality system. Examples of information sources for detecting precautionary measures related to the production process, equipment or plant include (WHO, 2013):

- In-process controls or quality controls (QC), which provide detailed trend data indicating that control limits are approaching. Precautionary measures include actions designed to return process performance to values away from the edges of the process control area.
- Supplier certification ,(e.g., % discarded materials or external audit findings)
- Complaints about product quality
- Changes in production efficiency e.g., due to defects of materials.
- Stability trend data
- Internal control cases
- Preventive maintenance warnings e.g., fail of equipment or use of spare parts
- Validation data (e.g., temperature profile shift in autoclave while still within acceptable range)

As depicted in Figure I.2.24, the strategy followed by the CAPA system begins with investigating variability, identifying the root cause, and possible response actions. The identified actions are then verified, approved, and implemented. Finally, they are evaluated based on their effectiveness. This is how the process is improved (WHO, 2013).

The third pillar of continuous improvement of performance and quality in ICH Q10 consists of the Change management System. Innovation, continuous improvement, the results of process performance and product quality monitoring as well as the CAPA system bring changes. In order for these changes to be properly evaluated, approved, and implemented, a company must have an effective change management system. The change management system ensures that continuous improvement is done in a timely and efficient manner. Depending on the stage of the life cycle it should include (International Council for Harmonisation, 2008):

- QRM to evaluate the proposed changes
- Proposed changes should be evaluated in relation to marketing authorization, including the design space where it is established, and / or the current understanding of the product and process.
- Proposed changes should be evaluated by teams of experts who contribute to the appropriate specialization and knowledge in related fields (e.g., Pharmaceutical Development, Industry, Quality, Medicine), to ensure that the change is technically justified.
- After implementation, the change must be evaluated to confirm that the objectives of the change have been achieved and that there has been no detrimental effect on product quality.

Table I.2.10: Application of Change Management System throughout the Product Lifecycle (International Council for Harmonisation Q10, 2008).

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Change is an inherent part of the development process and should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development.	The change management system should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science and risk-based assessments.	Any changes after product discontinuation should go through an appropriate change management system.

The fourth and final pillar of Directive Q10 is the management review of process performance and product quality. The review must first provide assurance that process performance and product quality are managed throughout the life cycle. Depending on the size and complexity of the company, the management review can be a series of reviews at different levels of management and must have a timely and effective communication and scaling process to highlight appropriate quality issues at senior management levels for review.

The management review system must include (International Council for Harmonisation, 2008):

- The results of inspections and findings, audits, and other evaluations, as well as commitments made to regulators.
- Periodic quality reviews, which may include:
    - Customer satisfaction measures (e.g., product quality complaints and recalls)
    - Conclusions on process performance and product quality monitoring
    - The effectiveness of changes in processes and products, including those resulting from corrective and preventive actions.
- Finally, it must include any follow-up actions from previous management reviews.

The Management review system should also identify appropriate actions such as (International Council for Harmonisation, 2008):

- Improvements in production processes and products
- Resource forecasting, training and / or review
- Collection and spread of knowledge

Table I.2.11: Application of Management Review of Process Performance and Product Quality throughout the Product Lifecycle (International Council for Harmonisation Q10, 2008).

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Aspects of management review can be performed to ensure adequacy of the product and process design.	Aspects of management review should be performed to ensure the developed product and process can be manufactured at commercial scale.	Management review should be a structured system, as described above, and should support continual improvement.	Management review should include such items as product stability and product quality.

Continual Improvement of PQS

In addition to the overview of process efficiency and product quality management, Directive Q10 describes the activities to be carried out to manage and continuously improve the pharmaceutical quality system.

The first part concerns the management review of the PQS. Initially, the management should have a formal procedure for the periodic review of the pharmaceutical quality system. The review should include:

- First, measuring the achievement of the objectives of the PQS.
- Second, the evaluation of performance indicators that can be used to monitor the effectiveness of procedures, such as: Complaints, deviations, CAPA and change management procedures, feedback on outsourced activities, Self-assessment procedures, including risk assessments, trends and controls, external assessments such as regulatory inspections and findings as well as customer audits.

The second step for the continuous improvement of the PQS is the monitoring of the internal and external factors that affect the system. Factors monitored by management may include:

- New regulations, guidance, and quality issues
- Innovations that could improve the system
- Changes in the business environment and goals
- Changes in product ownership

Finally, the results of the review of the quality management of the PQS and the monitoring of the external factors that affect the PQS are the last part of the continuous improvement of the system and may include:

- Improvements in the quality pharmaceutical system and related procedures.
- Allocation or redistribution of resources and / or staff training
- Quality policy reviews and quality objectives
- Documentation as well as timely and effective announcement of the results of the review and the actions of the management

I.2.4.4. The link between ICH Guidelines Q8, Q9 and Q10

Figure I.2.15 depicts the close connection between the ICH Directives Q8, Q9 and Q10.

Initially, the process of designing a product, a process, a distribution system, etc. begins and ends with the patient, and he should always be the guideline.

During the design and development phase, in-depth knowledge of the product, materials, equipment, and production process is provided. This knowledge must be described and recorded as only through it product and process understanding, reduction in quality risk and failures, and subsequent improvement can occur. This is the essence of the ICH Q8 directive and Quality by Design.

Directive Q10 tries to strengthen the link between development and production by introducing a model of an effective quality pharmaceutical system that promotes innovation and continuous improvement. The knowledge gained from the development can enable the effective implementation of this model.

Finally, both guidelines are complemented by the implementation of Quality Risk Management, ICH Q9, as it provides the principles and tools for assessing, controlling, spreading, and reviewing quality risks and enables more effective and consistent quality decisions to be made regarding medicinal products throughout their life cycle.

I.2.5. Comparison between Experimental Design and Traditional Experimental Methods

Experimental Design or Design of experiments (DoE) has been established widely in all fields of study as it is a powerful tool for experimentation. Through DoE, the effects that input variables have on output parameters can be identified through the least number of structured experiments and data acquisition (Islam and Pramanik, 2016). The different input parameters are varied simultaneously and through mathematical models, the effects on the output parameters are related to the changes and interactions of the inputs.

On the other hand, in traditional experimentation, usually one factor at a time is varied while the other factors remain fixed in order to investigate the effect of this particular factor at the output variable. This method even though is generally accepted, simple and easy conclusions are drawn, in reality, there is no assurance that these conclusions are correct and what happens if more than one input change simultaneously. Furthermore, in case the experimental result has not been achieved, this method does indicate in which direction the input variables need to be changed in order to achieve the desirable outcome.

Comparing one factor at a time (OFAT) and DoE approach, the latter is a more effective way to determine the impact of two or more factors on a response as (Czitrom, 1999):

- DoE requires less resources, e.g., number of experiments, time, materials, etc. for the amount of information obtained. This advantage is critical to the industry, where time and expenses of experiments play a key role.
- DoE is more precise in estimating the effects of each factor and their interactions because it uses more observations to estimate an effect, resulting in higher precision (reduced variability), while typically in OFAT less observations are used to estimate only the effect of each factor.
- DoE is capable to estimate interactions between factors systematically, while in OFAT interactions are not estimable.
- Through DoE, the experimental information obtained define the design space, in which the input factors can vary either without affecting the output variables driving them away from the desired target or by predicting the output due to this variation. Thus, DoE offers operating freedom, improved prediction, and process optimization. This is not possible with OFAT, as the solutions offered do not concern an operating space but set variables.

Another empirical experimentation method used in practice is the best-guess approach. In this method, an arbitrary set of input variables is chosen that theoretically is the best, and small changes in one or two factors is varied each time in order to optimize the output (Politis, 2010). This method works well in practice only deep theoretical and technical knowledge of the process is available. However, this is not only time consuming but also expensive. Moreover, there is no guarantee that the best solution has been found, as experiments can go on without any substantial optimization. Finally, after many guesses one tends to lose track of what guesses, or combinations of guesses, have already been tried.

The advantages and disadvantages when comparing DoE and OFAT are depicted in the following table (Politis, 2010).

Table I.2.12: Comparison of DoE vs OFAT (Politis, 2010; Singh et al., 2004).

DoE advantages	
• Require fewer experiments to achieve an optimum formulation.	• Can trace and rectify a "problem" in a remarkably easier manner.
• Yield the "best solution" in the presence of competing objectives.	• Lead to comprehensive understanding of the formulation system.
• Help in finding the "significant" and "non-significant" input variables.	• Tests and improves "robustness" amongst the experimental studies.
• Can change the formulation ingredients or processes independently.	• Aid in determining experimental error and detecting "bad data points."
• Can simulate the product or process behavior using model equation(s).	• Save a significant amount of resources viz. time, effort, materials, and cost.
• Evaluate and improve the statistical significance of the proposed model(s).	• Can predict the performance of formulations even without preparing them.
• Detect and estimate the possible interactions and synergies among variables.	• Facilitate decision–making before next experimentation by response mapping.
• Provide reasonable flexibility in experimentation to assess the product system.	• Can decouple signal from background noise enabling inherent error estimation.
• Comprehend a process to aid in formulation development and ensuing scale–up.	• Furnish ample information on formula behavior from one simultaneous study only.
OFAT disadvantages	
• Uneconomical. Time consuming.	• Strenuous.
• Unsuitable to plug errors.	• Inapt to reveal interactions.
• Pseudo-convergent to untrue optimum.	• Isolated and unconnected studies.
• Detailed study of all variables is prohibitive.	• Prone to misinterpretation or faking of results.
• Futile when all variables change simultaneously.	• Result only in "just satisfactory" solutions.
• Ineffectual as leads to unnecessary runs and batches.	• Unable to establish "cause and effect" relationship.
• Irreproducible as infers randomly on the basis of origin.	• New product may retain defects inherent in the old one.

I.2.6. Types of Experimental Designs

The various experimental designs can be categorized in the two different ways:

- According to the parameter under study:
  - Mixture designs
  - Factorial or process designs
  - Combination of Mixture-Process design
- According to the phase of the study:
  - Screening designs
  - Factor effect studies or process characterization design
  - Optimization or RSM designs

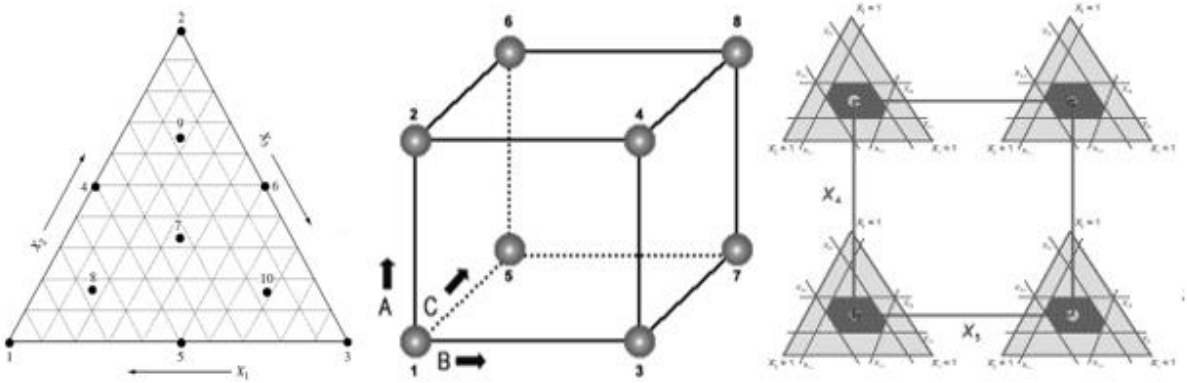


Figure I.2.26: Types of Experimental Designs according to the parameter under study: Left: Mixture Design, Middle: Factorial Design, Right: Combination of Mixture and Factorial Design (Πολίτης, 2010).

Mixture Designs

This type of designs is used in order to study the effect of the components of a pharmaceutical formulation when they are varied either qualitatively or quantitatively. They are applied when the total amount of the composition is certain, and their purpose is to characterize and/or optimize the use of each ingredient and its portion in the recipe. Typical examples of mixture designs are the quantification of an individual component of the composition of a tablet with specific total weight or the selection of the appropriate amount of solvents in a liquid formulation. It is obvious that in mixture designs the proportions of the ingredients are not independent of each other. This is because increasing one component, for example, necessarily reduces the other (s) so that the whole is kept constant. This leads to a dependent relationship between the selected responses as a function to the proportions of the components of the mixture.

Factorial or Process designs

This type of designs usually refers to parameters that affect processes and are adjusted independently of each other. In this case, the different parameters are altered in different sets of values (levels) in order to study how the response is affected either by each input variable or by their combinations. The responses are a function of the factor levels. Typical examples of input variables in process designs are the compression force and speed in tableting or the temperature, spray rate, incoming air pressure and volume in fluidized bed granulation.

Combination of Mixture-Process designs

In cases where it is needed to investigate the interactions between the ingredients of a recipe and process variables, a combination of mixture and process designs is used. In this type of designs a mixture design is performed at each level of the factorial design. Due to this fact, a large number of experiments is created and thus their application is rarer.

Screening Designs

These designs are implemented in an initial phase of experimenting when the target is to identify which of the factors under study are affecting the response in a statistically significant manner. During this phase, all potentially significant factors are screened in order to find the few important between the many non-significant. Factional factorial designs are mainly used at this point.

Factor effect studies or process characterization design

Apart from identifying the statistically significant factors, the target is to study the effects either positive or negative they have to the response or the interactions between the factors. This kind of design is usually carried out after a screening design has been completed or the initial factors are few, until three. The factor effect studies are described mainly by the full factorial designs, in which the main effects and all interactions between the factors are analyzed (Politis, 2010).

Optimization designs

The experiments that target optimization are designed with the use of the Response Surface Methodology (RSM). The aim of this methodology is the "mapping" of the response according to the changes in the factors, in order to find the variables or range of variables of the factors that lead to the optimized response (Georgaki et al., 2010).

I.2.6.1. Experimental Design terminology

The basic terms used when performing an experimental design are summarized below.

- Blocking: is a design technique used to improve the precision with which comparisons among the factors of interest are made. Blocking is a tool used to separate some expected variation from the analysis of the factor effects. Blocking screens out noise caused by known sources of variation, such as raw material batch, shift changes, or machine differences. It divides the experimental runs into homogeneous groups and then arithmetically removes the difference. Removing this block effect reduces the noise in the experiment, increasing the sensitivity of your DOE (Kraber, 1998; Montgomery, 2013).
- Effect: A change in a level of a factor may result in a change in the response. Thus, this factor has had an effect on the response. The effect is a calculated value of how much the response changes for a given change in the factor levels (Quallity Training Portal). This is frequently called a main effect because it refers to the primary factors of interest in the experiment (Montgomery, 2013).
- Factors: Are the independent variables of a process. Independent variables are the parameters or aspects of the process that can be set or change independently of the settings of another process variable. Factors can be related to people, equipment, methods, materials, and the environment (Quallity Training Portal).

- Interaction: Factors may influence each other causing different effects to the response than when the factors are alone; this is called an interaction. An interaction occurs when the response is different depending on the settings of the different factors (Kraber, 1998).
- Level: A level is a specific value or setting of a factor. Levels do not have to be variable measurements. They can also be attributes (Quallity Training Portal).
- Randomization: both the allocation of the experimental material and the order in which the individual runs of the experiment are to be performed are randomly determined. Statistical methods require that the observations (or errors) be independently distributed random variables. Randomization usually makes this assumption valid. By properly randomizing the experiment, we also assist in "averaging out" the effects of extraneous factors that may be present (Montgomery, 2013). Experiments set up by hand generally follow a very structured sequence, sometimes referred to as standard design order. The order in which you run the experiments should be randomized to avoid influence by time-related, uncontrolled, variables (Kraber, 1998).
- Replication: Replication is an independent repeat run of each factor combination. Replication is a tool used to improve the chance of detecting a statistically significant effect in the midst of natural process variation (Montgomery, 2013; Kraber, 1998; Quallity Training Portal).
- Response: The responses are the outputs of the process. Process outputs are dependent variables. Outputs, or responses, can be related to quality, product performance, productivity, or safety. Responses are the results of all of the actions of the independent variables, the factors (Kraber, 1998; Montgomery, 2013; Quallity Training Portal).

Other terms usually used at experimental design are reported in the following table (Politis, 2010).

Table I.2.13: Most usual terms in Experimental Design (Politis, 2010).

Experimental Design Terminology		
Blocking	Experimental space/domain	Qualitative factor
Blocks	Factor	Quantitative factor
Center points	Factor effect	Randomization
Coded variables	Factorial design	Replicates
Confirmatory runs	Interaction	Replication
Design in two levels	Level	Response
Effect	Level combination	Response surface methodology
Effect confounding or aliasing	Low/high level	Screening
Experiment	Mixtures	Sequential experimentation
Experimental design	Optimization	Significance
Experimental objective	Preliminary runs	Test
Experimental plan	Process model	Treatments combination
Experimental points		

I.2.6.2. Experimental Design methodology

Montgomery in his book "*Design and Analysis of Experiments"* (Montgomery, 2013) has proposed an procedure consisting of seven steps for the statistical approach in designing and analyzing an experiment. These seven steps are executed in three phases (Georgaki et al., 2010):

- Designing phase: During this phase, the recognition and target the experiment, the choice of response, factors, and their levels as well as the type of experimental design are selected.
- Execution phase: At this phase the actual experiments of the design are performed, and the responses are measured.
- Analysis and conclusion phase: Data obtained are analyzed and conclusions are drawn.

The seven step of the Experimental Design as proposed by Montgomery and are executed in the above phases are (Montgomery, 2013):

1. *Recognition of and statement of the problem*: The first step is to realize that a problem requiring experimentation exists and to develop a clear and generally accepted statement of this problem. The input from different parties such as management, engineering, quality assurance or operating personnel, in general a team approach is recommended. It is also useful to prepare a list of questions that are to be addressed by the experiment. A clear statement of the problem contributes to better understanding of the phenomenon being studied and the final solution of the problem.
2. *Selection of the response variable*: In selecting the response variable, the experimenter should be certain that this variable really provides useful information about the process under study. The experimenters must decide how each response will be measured, and address issues such as how will any measurement system be calibrated.
3. *Choice of factors, levels, and ranges*: At this step, the experimenter has to select the design factors, the ranges over which these factors will be varied and the specific levels at which the runs will be made. The potential factors that may influence the performance or system can be classified in various ways such as design factors, nuisance factors, constant factors, allowed to vary factors, controllable or uncontrollable factors. The experimenter has to choose which of these factors are of interest to study, which are controlled factors and can be kept constant or which are noise or uncontrolled factors. The design factors are the factors actually selected for study in the experiment. The experimenter also has to decide the range over which each factor will be varied and on how many levels of each variable to use. Process knowledge is required to do this, which is usually a combination of practical experience and theoretical understanding. When the objective of the experiment is factor screening or process characterization, it is usually best to keep the number of factor levels low, while the region of interest relatively large. As knowledge is obtained on which variables are significant over which levels, the region of interest can be narrowed in following experiments.
4. *Choice of experimental design:* Choice of design involves consideration of sample size (number of replicates), selection of a suitable run order for the experimental trials, and determination of whether or not blocking or other randomization restrictions are involved.
5. *Performing the experiment:* The basic principle of this step is to ensure that everything is conducted in accordance with the plan. Errors in experimental procedure at this stage will usually destroy experimental validity.
6. *Statistical analysis of the data:* Statistical methods should be used to analyze the data so that results and conclusions are objective. Software packages can be used for data statistical analysis or simple graphical methods, which are direct and easy to interpretate, or empirical models. It should be noted that all data are analyzed with a confidence interval estimate, thus suitable analysis techniques such as residual analysis and model adequacy checking should be included. Statistical techniques

coupled with good engineering or process knowledge and common sense will usually lead to sound conclusions.

7. *Conclusions and recommendations*: The last step is to draw practical conclusions about the results and recommend a course of action. Follow-up runs and confirmation testing should also be performed to validate the conclusions from the experiment.

The key message of this entire process is that experimentation is an important part of the learning process, in which a hypothesis about the system is formed, experiments are performed in order to accept this hypothesis or reject it and form a new one and repeat. During this repetitive process, knowledge about the important factors, the ranges over these factors should be varied and the levels to use is obtained, and as this continuous, some input variables are replaced by others, or the regions and levels vary. This leads to sequential experimentation. Thus, it is important the experiments are well-designed in order to have sufficient resources to accomplish the final objective of the experiment and not to waste time, money or other resources and result in poor and/or disappointing outcomes.

I.2.6.3. Mixture Designs

As mentioned in previous section, this type of designs is used in order to study the effect of the components of a pharmaceutical formulation when they are varied either qualitatively or quantitatively. They are applied when the total amount of the composition is certain, and their purpose is to characterize and/or optimize the use of each ingredient and its portion in the recipe. In mixture experiments, the factors are the components or ingredients of a mixture, and consequently their levels are not independent (Montgomery, 2013). For example, if $x_1, x_2, \ldots, x_p$ declare the proportions of p components of a mixture, then

$$0 \leq x_i \leq 1, \qquad i = 1,2,\ldots,p$$

and

$$x_1 + x_2 + \cdots + x_p = 1 \ \ (i.e.\, 100\ percent) \qquad \textit{Eq. I.2.1}$$

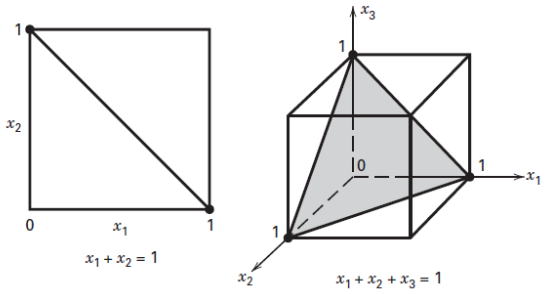


Figure I.2.27: Constrained factor space for mixtures with two components (left) and three components (right) (Montgomery, 2013).

For mixtures with two components, the factor space includes all values of the two components that lie on the line segment $x_1+x_2=1$, with each component being bounded by 0 and 1. With three components, the mixture space is a triangle with vertices corresponding to formulations that are pure blends (mixtures that are 100 percent of a single component) (Montgomery, 2013).

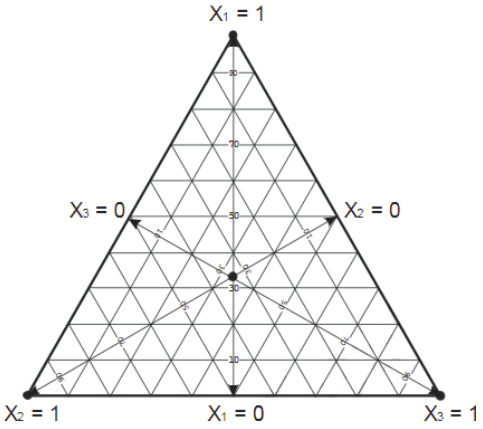


Figure I.2.28: Trilinear Coordinate System (Anderson et al., 2018; Montgomery, 2013).

As depicted in Figure I.2.28, in a three-component mixture, the constrained experimental region can be described by the trilinear coordinate system. Each corner in the triangle represents the 100% of the corresponding component in the mixture, meaning that the mixture consists of only one component (100% or 1 depending on how the mixture total is expressed). Each side of the triangle represents a mixture consisting only of two components (the component labeled on the opposite vertex is zero). Finally, the center of the triangle represents a three-component mixture with equal portions of each component (33.3%).

In order to study the components of a mixture on the response variable, ***Simplex designs*** are used. In particular, a {p, m} ***simplex lattice design*** for p components consists of points defined by (Montgomery, 2013):

$$x_i = 0, \frac{1}{m}, \frac{2}{m}, \ldots, 1 \quad where\ i = 1,2,\ldots,p \qquad Eq.\ I.2.2$$

The portions assumed by each component p, take the m+1 equally spaced value from 0 to 1 and all possible combinations (mixtures) of the proportions. For example, when p=3 and m=2, then x_i = 0, ½, 1 for i=1,2,3, and the simplex lattice consists of 6 runs: (x1,x2,x3) = (1,0,0), (0,1,0), (0,0,1), (1/2,1/2,0), (1/2,0,1/2), (0,1/2,1/2). Examples of simplex lattice designs for 3 and 4 components are depicted in the following figure (Anderson et al., 2018).

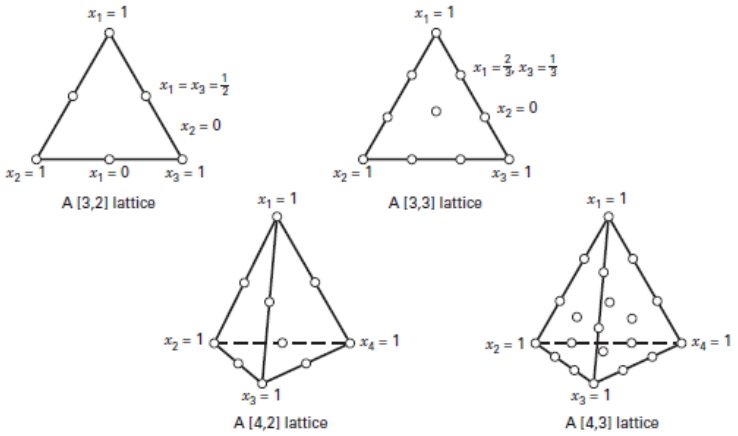


Figure I.2.29: Simplex lattice designs for three and four components (Montgomery, 2013).

The vertices that describe the pure blends are (1,0,0), (0,1,0) and (0,0,1), whereas binary blends are described by (1/2,1/2,0), (1/2,0,1/2) and (0,1/2,1/2) vertices, located at the middle of the three sides of the triangle. For four components, the constrained experimental region is described by a tetrahedron, as shown in the above figure. In general, the number of points in a {p, m} simplex lattice design is calculated by the following equation (Montgomery, 2013):

$$N = \frac{(p+m-1)!}{m!(p-1)!} \qquad \textit{Eq. I.2.3}$$

Apart from simplex lattice designs, *simplex centroid designs* are also used, in which 2^p-1 points exist, corresponding to the p permutations of (1, 0, 0, …, 0), the $\binom{p}{2}$ permutations of (½, ½, 0, …, 0), the $\binom{p}{3}$ permutations of (1/3, 1/3, 1/3, 0, …, 0), …, and the overall centroid (1/p, 1/p, …, 1/p) as depicted in the following figure.

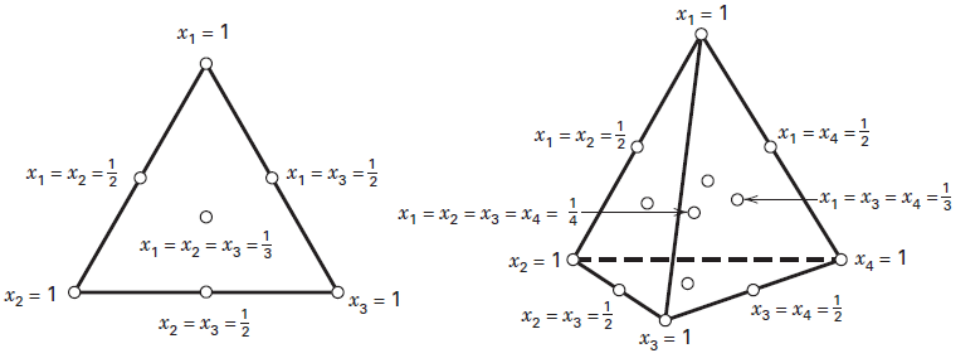
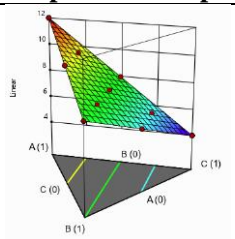
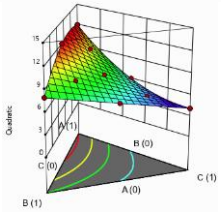


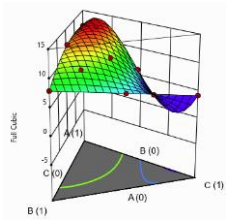
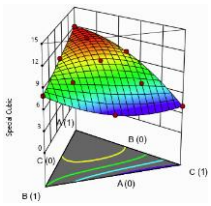
Figure I.2.30: Simplex centroid designs with three (left) and four (right) components (Montgomery, 2013).

In this type of designs, either simplex lattice or centroid, it is recommended to augment the design by adding additional points in the interior of the region, in order to include all p mixture components, as most of the experimental runs normally occur on the boundary of the region, including only p - 1 of the components (Montgomery, 2013).

The most commonly used forms of mixture models are (Montgomery, 2013):

Table I.2.14: Most common mixture models (Montgomery, 2013; Stat-Ease Inc., 2021).

Model	Model equation	Graphical example
Linear	$E(y) = \sum_{i=1}^{p} \beta_i x_i$ *Eq. I.2.4*	
Quadratic	$E(y) = \sum_{i=1}^{p} \beta_i x_i + \sum\sum_{i<j}^{p} \beta_{ij} x_i x_j$ *Eq. I.2.5*	

Model	Model equation	Graphical example
Full cubic	$E(y) = \sum_{i=1}^{p} \beta_i x_i + \sum\sum_{i<j}^{p} \beta_{ij} x_i x_j + \sum\sum_{i<j}^{p} \delta_{ij} x_i x_j \left(x_i - x_j\right) + \sum\sum\sum_{i<j<k} \beta_{ijk} x_i x_j x_k$ *Eq. I.2.6*	
Special cubic	$E(y) = \sum_{i=1}^{p} \beta_i x_i + \sum\sum_{i<j}^{p} \beta_{ij} x_i x_j + \sum\sum\sum_{i<j<k} \beta_{ijk} x_i x_j x_k$ *Eq. I.2.7*	

The parameter β_i represents the expected response to the pure blend $x_i=1$ and $x_j=0$ when $j \neq i$. The portion $\sum_{i=1}^{p} \beta_i x_i$ is called the linear blending portion. When curvature arises from nonlinear blending between component pairs, the parameters β_{ij} represent either synergistic or antagonistic blending (Montgomery, 2013).

When augmenting the simplex designs with additional axial runs and the overall centroid, the model can make predictions about the properties of complete mixtures as shown in Figure I.2.31. This figure shows the {2, 3} simplex lattice design augmented with the axial check blends, at which the axial runs are places midway between the centroid of the simplex and each vertex, so that $\Delta=(p-1)/2p$, where Δ is the distance from the centroid. This design has 10 points, three at the corners of the triangle representing the pure blends, the points at the middle of each triangle side representing the binary mixtures, the centroid and three points in the interior of the simplex. The augmented simplex lattice is superior to the simplex lattice for studying the response of complete mixtures as it can detect and model curvature in the interior of the triangle. Also, the augmented simplex lattice has more power for detecting lack of fit (Montgomery, 2013).

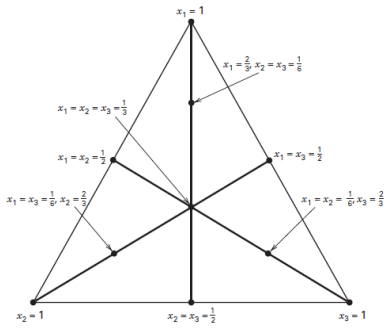


Figure I.2.31: Augmented simplex lattice design (Montgomery, 2013).

In cases where constrains on the individual components exist, the design region changes. If, lower bound constrains are present, $l_i \leq x_i \leq 1\,, where\ i = 1, 2, .., p$, then the design region even though is still a simplex, it falls within the original simplex region. In this case, pseudo-components can be used, which allow the transformation of the original components. Pseudo-components are defined as (Montgomery, 2013):

$$x_i' = \frac{x_i - l_i}{\left(1 - \sum_{j=1}^{p} l_j\right)} \; with \sum_{j=1}^{p} l_j < 1 \qquad Eq.\ I.2\ 8$$

Now $x_1' + x_2' + \cdots + x_p' = 1$

By reversing this transformation, the original components can be calculated using the following equation (Montgomery, 2013):

$$x_i = l_i + \left(1 - \sum_{j=1}^{p} l_j\right) x_i' \qquad Eq.\ I.2.9$$

An example of a mixture with three components, at which a lower bound constrain is applied to either one, two or all three components is depicted in Figure I.2.32.

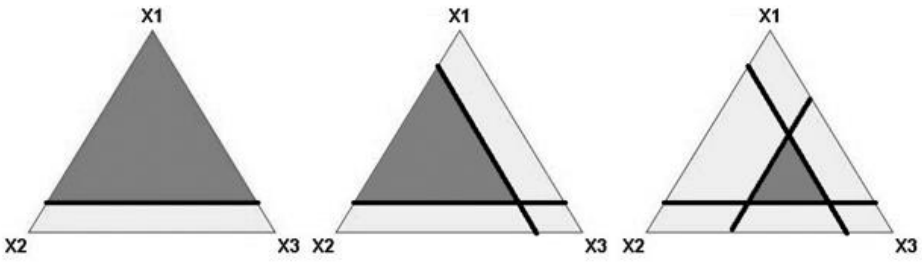


Figure I.2.32: Mixture with three components and lower bound constrain in one component X_1 (left), in two components X_1 and X_2 (middle) and three components X_1, X_2 and X_3 (right) (Politis, 2010).

In case the components of a mixture have both lower and upper bound constraints, the design region is no longer a simplex but an irregular polytope and computer-generated optimal designs are used for this type of experiments (Montgomery, 2013). In more detail, the computer generates a series of points within the irregular design region and based on a specific algorithm for model optimization, picks some of these points and correlates the variables of the mixture components and the responses. The selection of these points is either based on the accuracy of the coefficients of the models or the ability of the model to predict the response within the design region. A-optimal and D-optimal designs belong to the first category, while V-optimal and G-optimal designs belong to the second category (Politis, 2010).

Screening designs are constructed to estimate linear effects (gradients) to determine which ingredients will be included in future experiments. Component ranges determine if simplex or non-simplex design interface is provided. These designs allow you to look at a large number of components in a minimal number of blends, revealing the important components - positive or negative. The goal of a mixture screening experiment is to use as few runs as possible to decide which components will be studied in more detail during the latter phases of the experimentation process. However, they do not give much information about interactions. Ideally, the screening designs lead to a reduction in components (Stat-Ease Inc., 2021).

Optimal (custom) designs work with unequal component ranges, multi-component constraints, blocking, custom models, and specific augments. Run settings are chosen algorithmically to provide the best estimates for the chosen model. By default, optimal designs are augmented with five lack of fit and five replicates. The lack of fit runs are picked to maximize the minimum distance to other runs, while not being overly damaging to the optimality. The replicates are used to estimate pure error, or the variability in the results even though the factor settings did not change. (Stat-Ease Inc., 2021).

I.2.6.4. Factorial Designs

General Factorial Designs

Factorial design is an experimental strategy in which factors are varied together, instead of one at a time, making the most efficient use of the experimental data. In each complete trial or replicate of the experiment in factorial designs, all possible combinations of the levels of the factors are investigated. For example, if there are *a* levels of factor A and *b* levels of factor B, each replicate contains all *ab* treatment combinations (Montgomery, 2013). An example of two-factor factorial experiment with both design factors at two levels is depicted in the following figure.

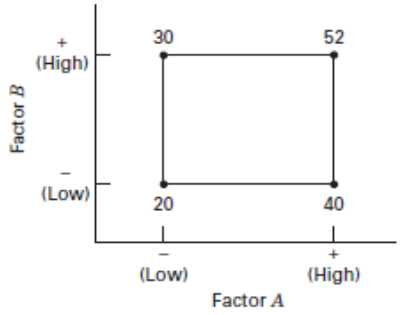


Figure I.2.33: Graphical representation of a two-factor factorial experiment with both design factors (A, B) at two levels (low:- , high: +) and the response shown at the corners (Montgomery, 2013).

When the effect of one factor depends on the level chosen for the other factors, there is an interaction between these factors, and this can be illustrated graphically as depicted in Figure I.2.34 for a two-factor factorial experiment with both design factors at two levels.

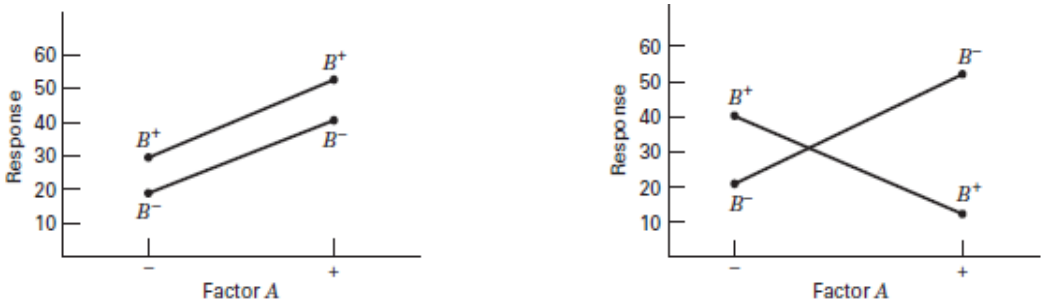


Figure I.2.34: Interactions plot for factorial experiments. Left: lack of interaction, right: with interaction (Montgomery, 2013).

The left figure illustrates the response data against factor A for both levels of factor B. The lines are approximately parallel, indicating lack of interaction between factors A and B. Similarly, on the right, the lines are not parallel indicating an interaction between the two factors (Montgomery, 2013).

A two-factor factorial design is the simplest type of factorial design, involving only two factors e.g., A and B at *a* levels for factor A and *b* levels for factor B, while each replicate *n* of the experiment contains all *ab* combinations. Generalizing this case, if y_{ijk} is the observed response when factor A is at the *i*th level (i=1,2, …, a) and factor B is at its *j*th level (j=1,2, …, b) for the *k*th replicate (k=1,2, …, n) then the two-factor factorial design is presented as depicted in the following table. The order in which the *abn* observations are taken is selected at random so that this design is a completely randomized design.

Table I.2.15: Representation of Two-Factor Factorial Design (Montgomery, 2013).

		Factor B			
		1	2	…	b
Factor A	1	$y_{111}, y_{112}, \ldots, y_{11n}$	$y_{121}, y_{122}, \ldots, y_{12n}$		$y_{111}, y_{112}, \ldots, y_{11n}$
	2	$y_{211}, y_{212}, \ldots, y_{21n}$	$y_{221}, y_{222}, \ldots, y_{22n}$		$y_{111}, y_{112}, \ldots, y_{11n}$
	⋮				$y_{111}, y_{112}, \ldots, y_{11n}$
	a	$y_{a11}, y_{a12}, \ldots, y_{a1n}$	$y_{a21}, y_{a22}, \ldots, y_{a2n}$		$y_{ab1}, y_{ab2}, \ldots, y_{abn}$

A model that can describe the factorial experiment is the ***effects model***, represented by

$$y_{ijk} = \mu + \tau_i + \beta_j + (\tau\beta)_{ij} + \varepsilon_{ijk} \begin{cases} i = 1, 2, \ldots, a \\ j = 1, 2, \ldots, b \\ k = 1, 2, \ldots, n \end{cases} \qquad \textit{Eq. I.2. 10}$$

Where μ is the overall mean effect, τ_i is the effect of the *i*th level of the row factor A, β_j is the effect of the *j*th level of column factor B, $(\tau\beta)_{ij}$ is the effect of the interaction between τ_i and β_j, and ε_{ijk} is a random error component. Both factors are assumed to be fixed, and the treatment effects are defined as deviations from the overall mean, so $\sum_{i-1}^{\alpha} \tau_i = 0$ and $\sum_{j-1}^{\beta} \beta_j = 0$. Similarly, the interaction effects are fixed and are defined such that $\sum_{i-1}^{\alpha} (\tau\beta)_{ij} = \sum_{j-1}^{\beta} (\tau\beta)_{ij} = 0$. Because there are *n* replicates of the experiment, there are *abn* total observations (Montgomery, 2013).

Another model describing the factorial experiment is the ***means model***, represented by (Montgomery, 2013):

$$y_{ijk} = \mu_{ij} + \varepsilon_{ijk} \begin{cases} i = 1, 2, \ldots, a \\ j = 1, 2, \ldots, b \\ k = 1, 2, \ldots, n \end{cases} \qquad \textit{Eq. I.2 11}$$

Where the mean of the *ij*th cell is $\mu_{ij} = \mu + \tau_i + \beta_j + (\tau\beta)_{ij}$ *Eq. I.2.12*

In the two-factor factorial, both row and column factors, A and B, are of equal interest. Specifically, the testing of hypotheses about the equality of factor A (row) effects is expressed as (Montgomery, 2013):

$$H_0: \tau_1 = \tau_2 = \cdots = \tau_\alpha = 0$$
$$H_1: at\ least\ one\ \tau_i \neq 0 \qquad \textit{Eq. I.2.13}$$

and the equality of factor B (column) effects is expressed as (Montgomery, 2013):

$$H_0: \beta_1 = \beta_2 = \cdots = \beta_b = 0$$
$$H_1: at\ least\ one\ \beta_j \neq 0 \qquad \textit{Eq. I.2.14}$$

The possible interaction between the two factors is determined by the following test (Montgomery, 2013):

$$H_0: (\tau\beta)_{ij} = 0, for\ all\ i, j$$
$$H_1: at\ least\ one\ (\tau\beta)_{ij} \neq 0 \qquad \textit{Eq. I.2.15}$$

These hypotheses are rested using the two-factor analysis of variance (ANOVA). The ANOVA for the Two-Factor factorial, fixed effects model is depicted in Table I.2.16.

Table I.2.16: Analysis of Variance (ANOVA) table for Two-Factor Factorial, Fixed Effects Model (Montgomery, 2013)

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F_0
Factor A	SS_A	a – 1	$MS_A = \frac{SS_A}{a-1}$	$F_0 = \frac{MS_A}{MS_E}$
Factor B	SS_B	b – 1	$MS_B = \frac{SS_B}{b-1}$	$F_0 = \frac{MS_B}{MS_E}$
Interaction	SS_{AB}	(a – 1) (b – 1)	$MS_{AB} = \frac{SS_{AB}}{(a-1)(b-1)}$	$F_0 = \frac{MS_{AB}}{MS_E}$
Error	SS_E	ab (n – 1)	$MS_E = \frac{SS_E}{ab(n-1)}$	
Total	SS_T	abn – 1		

By extending the two-factor factorial design to a more general case where there are A, B, C and so on factors with a, b, c, … levels respectively, and abc, …, n total observations with n replicates, the ANOVA can be used for testing the hypothesis for the main effects and interactions. For three-factor analysis, Equation I.2.10 is varied as:

$$y_{ijkl} = \mu + \tau_i + \beta_j + \gamma_k + (\tau\beta)_{ij} + +(\tau\gamma)_{ik} + (\beta\gamma)_{jk} + +(\tau\beta\gamma)_{ijk} + \varepsilon_{ijkl} \begin{cases} i = 1, 2, \dots, a \\ j = 1, 2, \dots, b \\ k = 1, 2, \dots, c \\ l = 1, 2, \dots, n \end{cases} \quad \textit{Eq. I.2 16}$$

The ANOVA table for Three-Factor fixed effects model is expressed as shown in Table I.2.17.

Table I.2.17: Analysis of Variance (ANOVA) table for Three-Factor Factorial, Fixed Effects Model (Montgomery, 2013)

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	Expected Mean Square	F_0
A	SS_A	a – 1	MS_A	$\sigma^2 + \frac{bcn\sum\tau_i^2}{a-1}$	$F_0 = \frac{MS_A}{MS_E}$
B	SS_B	b – 1	MS_B	$\sigma^2 + \frac{acn\sum\beta_j^2}{b-1}$	$F_0 = \frac{MS_B}{MS_E}$
C	SS_C	c – 1	MS_C	$\sigma^2 + \frac{abn\sum\gamma_k^2}{c-1}$	$F_0 = \frac{MS_C}{MS_E}$
AB	SS_{AB}	(a – 1) (b – 1)	MS_{AB}	$\sigma^2 + \frac{cn\sum\sum(\tau\beta)_{ij}^2}{(a-1)(b-1)}$	$F_0 = \frac{MS_{AB}}{MS_E}$
AC	SS_{AC}	(a – 1) (c – 1)	MS_{AC}	$\sigma^2 + \frac{bn\sum\sum(\tau\gamma)_{ik}^2}{(a-1)(c-1)}$	$F_0 = \frac{MS_{AC}}{MS_E}$
BC	SS_{BC}	(b – 1) (c – 1)	MS_{BC}	$\sigma^2 + \frac{an\sum\sum(\beta\gamma)_{jk}^2}{(b-1)(c-1)}$	$F_0 = \frac{MS_{AC}}{MS_E}$
ABC	SS_{ABC}	(a – 1) (b – 1)(c – 1)	MS_{ABC}	$\sigma^2 + \frac{n\sum\sum\sum(\tau\beta\gamma)_{ijk}^2}{(a-1)(b-1)(c-1)}$	$F_0 = \frac{MS_{ABC}}{MS_E}$
Error	SS_E	abc (n – 1)	MS_E	σ^2	
Total	SS_T	abcn – 1			

The Two-level (2^k) Factorial Designs

In this type of designs, there are k factors, each at only two levels, which can be either quantitative or qualitative. The factorial design would require 2^k runs, thus it is called two-level or 2^k factorial design. The 2^k design is particularly useful in the early stages of experimental work when many factors are likely to be investigated. It provides the smallest number of runs with which k factors can be studied in a complete factorial design. Consequently, these designs are widely used in factor screening experiments. The assumptions of this class if designs are that (Montgomery, 2013):

- The factors are fixed
- The design in completely randomized
- The normality assumptions are satisfied

For two factors (A, B) and the 2 levels, "low" (-) and "high" (+), the 2^2 factorial design, would require four runs, namely a (A high, B low levels), b (A low, B high levels), ab (both A,B at high levels) and 1 (both A,B at low levels), as depicted in Figure I.2.35.

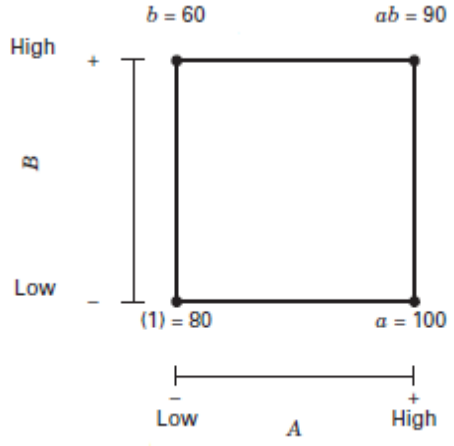
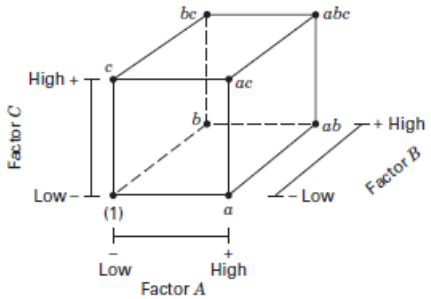


Figure I.2.35: Graphical representation of 2^2 factorial design (Montgomery, 2013).

For three factors (A, B, C) at two levels each, "low" (-) and "high" (+), the 2^3 factorial design, would require eight runs, displayed geometrically as a cube, as shown in Figure I.2.35.



Run	Factor A	B	C
1	–	–	–
2	+	–	–
3	–	+	–
4	+	+	–
5	–	–	+
6	+	–	+
7	–	+	+
8	+	+	+

Figure I.2.36: Graphical representation of 2^2 factorial design (left) and design matrix (right) (Montgomery, 2013).

The representation of the runs required for the 2^k designs is called the design matrix and uses different notations to explain the different factor combinations at each level. For example, the + and – notation is called geometric coding or orthogonal coding or the effects coding, the second notation uses lowercase

letter labels, and the final notation uses 1 and 0 to denote high and low factor levels, instead of + and – . An example of the design matrix with different notations for 2^3 designs, is illustrated in Table I.2.18

Table I.2.18: Design matrix for 2^3 factorial design (Montgomery, 2013).

Run	A	B	C	Labels	A	B	C
1	–	–	–	(1)	0	0	0
2	+	–	–	a	1	0	0
3	–	+	–	b	0	1	0
4	+	+	–	ab	1	1	0
5	–	–	+	c	0	0	1
6	+	–	+	ac	1	0	1
7	–	+	+	bc	0	1	1
8	+	+	+	abc	1	1	1

The main effects and interactions for such 2^3 factorial designs are depicted in Figure I.2.37.

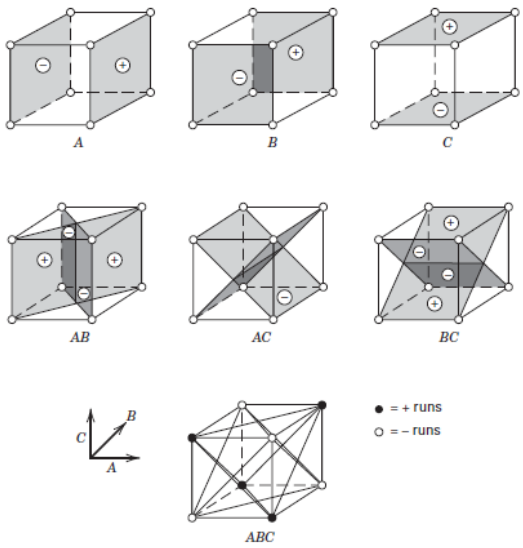


Figure I.2.37: Geometric representation of main effects (top), two factor interactions (middle) and three-factor interaction (bottom) (Montgomery, 2013).

Generalizing the design to k factors at 2 levels (2^k factorial design), the statistical model would include k main effects, $\binom{k}{2}$ two-factor interactions, $\binom{k}{3}$ three-factor interactions, …, and one k-factor interaction. Thus, the complete model would contain $2^k - 1$ effects for a 2^k design. The general approach to the statistical analysis for the 2^k design includes the following steps (Montgomery, 2013):

1. Estimate factor effects
2. Form initial model
    a. If the design is replicated, fit the full model
    b. If there is no replication, form the model using probability plot of the effects
3. Perform statistical testing (ANOVA)
4. Refine model
5. Analyze residuals
6. Interpret results

The ANOVA for a 2^k design is illustrate in the following table (Montgomery, 2013).

Table I.2.19: ANOVA for a 2^k Design. (Montgomery, 2013).

Source of Variation	Sum of Squares	Degrees of Freedom
k main effects		
A	SS_A	1
B	SS_B	1
⋮	⋮	⋮
K	SS_K	1
$\binom{k}{2}$ two-factor interactions		
AB	SS_{AB}	1
AC	SS_{AC}	1
⋮	⋮	⋮
JK	SS_{JK}	1
$\binom{k}{3}$ three-factor interactions	⋮	⋮
ABC	SS_{ABC}	1
ABD	SS_{ABD}	1
⋮	⋮	⋮
IJK	SS_{IJK}	1
⋮	⋮	⋮
$\binom{k}{k}$ k-factor interactions		
ABC ⋯ K	$SS_{ABC\cdots K}$	1
Error	SS_E	$2^k(n-1)$
Total	SS_T	$n2^k - 1$

A useful tool or method of analysis to identify the main effects in a data set is the normal probability plot of the estimates of the effects. The effects that are negligible are normally distributed, with mean zero and variance σ^2 and will tend to fall along a straight line on this plot, whereas significant effects will have nonzero means and will not lie along the straight line. Thus, the preliminary model will be specified to contain those effects that are apparently nonzero, based on the normal probability plot. The apparently negligible effects are combined as an estimate of error. An example of normal probability plot of estimates for a 2^4 design is depicted in Figure I.2.38 (Montgomery, 2013).

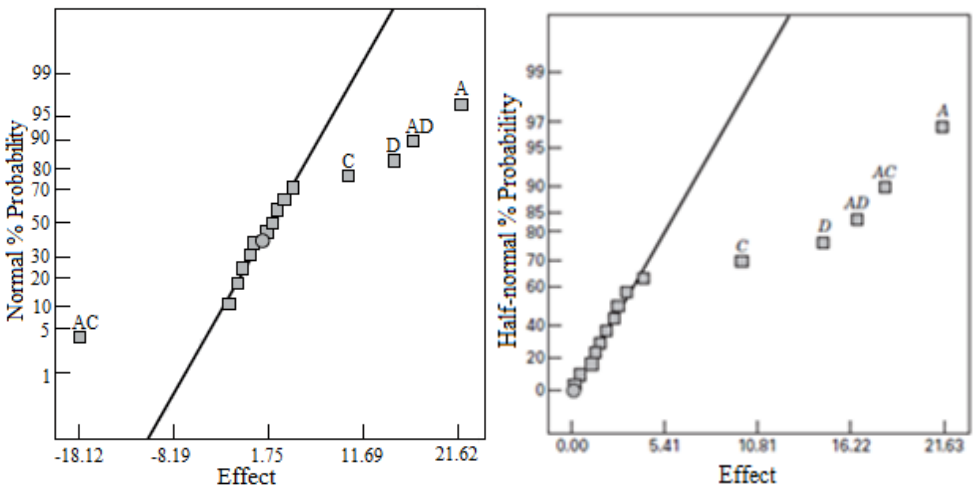


Figure I.2.38: Normal probability plot of effects for the 2^4 factorial design (Left) and Half-normal probability plot of effects for the 2^4 factorial design (right) (Montgomery, 2013).

The Half-Normal Plot of Effects depicted in Figure I.2.38 is an alternative to the normal probability plot of the factor effects. At this kind of plot, the absolute value of the effect estimates is against their cumulative normal probabilities. The straight line on the half-normal plot always passes through the origin and should also pass close to the fiftieth percentile data value. This plot is easier to interpret in simpler designs such as an eight-run design as there are only a few effect estimates (Montgomery, 2013).

Another graphical tool used to manage model selection for two-level factorial designs and identify the main effects is the Pareto chart. The primary use of the Pareto chart is to check for "the more significate effect" that was not obvious on the half-normal plot. There are two different t limits plotted on the graph. The highest limit is based on the Bonferroni or family-wise corrected t-critical value. The lower limit is based on standard t-critical for individual effects tests. The limits are re-calculated as the terms selected for the model are changed. The selected effects that are above the Bonferroni limit are almost certainly important and should be left in the model. Effects that are above the t-value Limit are possibly important and should be added if they make sense to the experimenter. Effects that are below the t-value limit should only be selected to support hierarchy. An example of a Pareto chart is shown in Figure I.2.39 (Stat-Ease Inc., 2021).

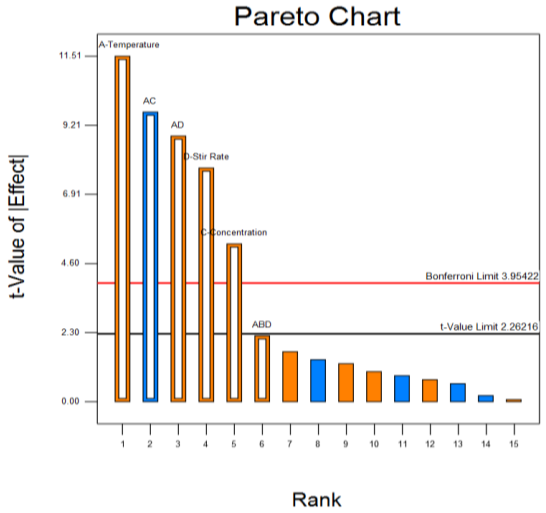


Figure I.2.39: Example of a Pareto Chart (Stat-Ease Inc., 2021).

The Addition of Center Points to the 2^k Design

In the two-level factorial designs, it is assumed that the effects in the factors are linearly correlated. If interaction terms are added to the main effect or first-order model, then the model is capable of representing some curvature in the response function as shown in $y = \beta_0 + \sum_{j=1}^{k} \beta_j x_j + \sum_{i<j} \sum \beta_{ij} x_i x_j + \varepsilon$ Eq. I.2.17, where $\beta_{ij}x_ix_j$ are the interaction terms (Montgomery, 2013).

$$y = \beta_0 + \sum_{j=1}^{k} \beta_j x_j + \sum_{i<j} \sum \beta_{ij} x_i x_j + \varepsilon \qquad \textit{Eq. I.2.17}$$

In some cases, curvature is not adequately represented by this equation, thus another model is necessary, which includes quadratic affects. This model is called second-order response surface model and is expressed by the following equation (Montgomery, 2013).

$$y = \beta_0 + \sum_{j=1}^{k} \beta_j x_j + \sum_{i<j} \sum \beta_{ij} x_i x_j + \sum_{j=1}^{k} \beta_{jj} x_j^2 + \varepsilon \qquad \textit{Eq. I.2.18}$$

In a 2^k factorial design, it is possible to add center points which will provide information on the existence of curvature to the model, thus quadratic effects. If a 2^k factorial design with additional center points is augmented with axial runs, the resulted design called central composite can be used to fit the second-order model. An example of a central composite design for k=2 and k=3 factors is shown in the following figure (Montgomery, 2013).

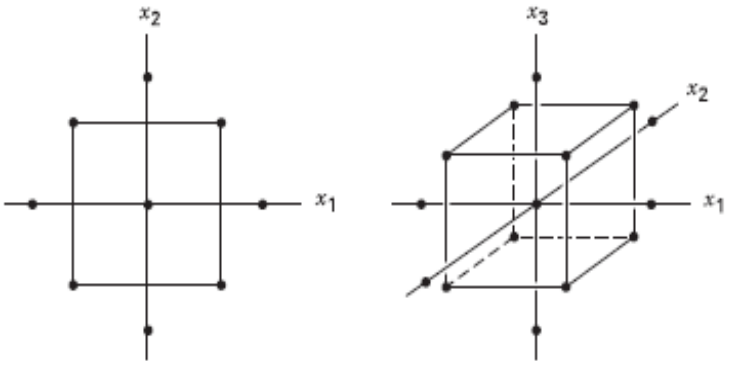


Figure I.2.40: Central composite design for two factors (left) and three factors (right) (Montgomery, 2013).

Coded Design Variables

In many cases, the analysis and model fitting for the 2^k factorial designs are performed using coded variables in the range of $-1 \leq x_i \leq +1$ instead of the original, actual units. The coded variables are used as the obtained numerical results are easier to interpret in contrast to the original data. In the coded variable analysis, the magnitudes of the model coefficients are directly comparable, as they are all dimensionless, and they measure the effect of changing each design factor over a one-unit interval. Furthermore, they are all estimated with the same precision. Coded variables are very effective for determining the relative size of factor effects. On the other hand, when using the actual unit data, the regression coefficients are not dimensionless and are estimated with differing precision. The actual units are not directly comparable, but they have physical meaning. Generally, the coded variables allow the easier identification of the relative importance of the design factors (Montgomery, 2013).

Two-Level Fractional Factorial Designs

In 2^k factorial designs the number of runs depends on the number of factors and as the factors increase, the number of runs also increase, from which, only a few portion relates to the main effects or two-factor interactions, while the remaining runs are correlated to higher order interactions and are of less interest. If it is assumed that for a particular case that the information from the main effects and low-order interactions are of importance and the high-order interactions are negligible, then a fraction of the complete factorial design can be run. A fractional factorial experiment is a variation of the basic factorial design in which only a subset of the runs is used. These fractional factorial designs are among the most widely used types of designs for product and process design, process improvement, and industrial/business experimentation (Montgomery, 2013).

Fractional factorial designs are mostly used in screening experiments, in which the target is to identify the major factors among many potentially significant factors. The three key ideas that fractional factorial designs are based are (Montgomery, 2013):

1. The sparsity of effects principle: Some of the main effects and low order interactions are more likely to drive the system or process when there are several variables. According to this principle, only 20% of the main effects and interactions of two factors may be significant in a system or process.
2. The projection property: Fractional factorial designs can be projected into stronger (larger) designs in the subset of significant factors.
3. Sequential experimentation: Different fractional factorial designs can be combined to construct sequentially a larger design to estimate the main effects and interactions. Meaning that a fractional factorial design can be the first step in an experiment, indicating how the following designs need to be constructed to reach the final target.

Subcategories of fractional factorial designs are the one-half Fraction (2^{k-1}), the on-fourth fraction (2^{k-2}), the one-eighth fraction (2^{k-3}) and so on. Due to their construction, in fractional factorial designs cofounding of the terms is present, thus their interactions cannot be estimated independently. These terms are then aliased. Thus, it is important to identify the aliased terms and to ensure that the main interactions are mot confounded with insignificant interactions. In fractional factorial designs, the design resolution plays a key role in the interpretation of the results as depending on the resolution, confounded terms are neglected. Design resolution is symbolized as a Latin letter and is indicated to the design as index, e.g., 2_{III}^{3-1}. The main design resolutions are (Montgomery, 2013):

- Resolution III designs: Main effects are aliased with two-factor interactions and some two-factor interactions may be aliased with each other, but no main effects are aliased with any other main effect. The 2^{3-1} design is of resolution III (2_{III}^{3-1}).
- Resolution IV designs: Two-factor interactions are aliased with each other, but no main effect is aliased with any other main effect or with any two-factor interaction. A 2^{4-1} design is a resolution IV design (2_{IV}^{4-1}).
- Resolution V designs: Two factor interactions are aliased with three-factor interaction, but no main effect or two-factor interaction is aliased with any other main effect or two-factor interactions. A 2^{5-1} design is a resolution V design (2_{V}^{5-1}).

Resolution V designs are the most desired type in terms of cofounded terms but require more runs thus are more expensive than resolution IV designs and resolution III designs.

Custom Factorial Designs

In some situations, the requirements of the standard factorial and fractional factorial designs cannot fit to the research problem. Some of these include (Montgomery, 2013; Stat-Ease Inc., 2021):

- Unusual resource restrictions, e.g., the number of runs or the size of blocks are different from the standard design.
- Restrictions or constrains on the design space.
- There is a need to fit a nonstandard model, e.g., a model that contains a mix of factors of different types (numeric and categoric factors).
- A higher than quadratic order model is necessary to estimate the response surface.
- Replicates need to spread throughout the design rather than only the center point.
- Difference between the high and low of all the components not the same.
- Mixture and process variables in the same design.
- Too many runs in the standard designs.
- Data has already been gathered.
- Combinations of the above.

Thus, the experimenter needs to adopt a different kind of approach, called a custom design, that fits to the specific problem. Creating a custom design requires (Montgomery, 2013):

- Information about the problem, e.g., the region of interest, the number of runs, the model etc.
- Choosing an optimality criterion, meaning a criterion for selecting the design points to run
- A software package to construct the design.

It is always better to create a custom design for the actual problem to be solved rather than force the problem to fit a standard design (Montgomery, 2013).

The number of runs in custom designs depends on the number of terms in the model, the number of blocks and the number of additional models, lack of fit, replicates and centroids requested during the build.

Design Optimality Criterion

There are three design optimality criteria (Montgomery, 2013):

- *D-optimality:* A design that minimizes the variance of the model regression coefficients is called a D-optimal design. In these designs, the criterion with which the designs points are selected minimizes the volume of the joint confidence region of the regression coefficients, by maximizing the determinant of the X'X matrix (hence "D"). For example, the 2^k design is a D-optimal design for fitting the first-order model or the first-order model with interaction. In general, controlling the volume of the confidence region is related to the precision of the regression coefficients; a smaller confidence region, for the same level of confidence, means more precise estimates.
- *G-optimality*: G-optimal designs minimize the maximum value of prediction variance in the design region.

- *I-optimality:* The I-optimal design minimizes the integrated or average prediction variance of the regression model over the design region

The most widely used optimality criteria are the D and I optimality. Many software packages crease designs that are based to these criteria an made use of optimization algorithms such as coordinate and point exchange.

The *Coordinate Exchange algorithm* builds an approximately optimal design as (Stat-Ease Inc., 2021):

1. Select a random initial set of points equal to the number of terms in the design to be modeled. This random selection is done by:
    - Start with a random coordinate (point) within the design space.
    - Randomly pick each subsequent design point and evaluate if it increases the rank of the matrix.
    - Continue this process until a full rank matrix is obtained.
2. Randomly select any extra model points.
3. Start the coordinate exchange algorithm.
    - Calculate the current optimality criterion.
    - Sort the points by contribution to the optimality criterion.
    - Starting with the worst point, move it along a set of directions in incremental steps.
    - If the optimality criterion improves, change the point, and move on to the next point in the list
    - If the optimality criterion does not improve, retain the point, and move on to the next point
    - Once the entire list is exhausted, restart the algorithm
    - If all points are retained, then they form a locally optimal design.
    - Repeat the algorithm several times to improve the odds of finding the globally optimal design.
4. Lack-of-fit points are added to the design to fill the largest gaps by selecting a group of points that maximizes the minimum distance to another point.
5. Replicates are chosen that best support the optimality criterion.
6. Additional centroids, if any, are added.

The *Point Exchange algorithm* builds an approximately optimal design as follows (Stat-Ease Inc., 2021):

1. Define a candidate set of possible factor combinations.
2. Select a random initial set of points from the above candidate set equal to the number of terms in the design to be modeled:
    - Start with a random point from the candidate set.
    - Randomly pick each subsequent design point.
    - If a new point increases the rank of the matrix point it is added to the starting bootstrap.
    - Continue this process until a full rank matrix is obtained.
3. Randomly select any extra model points.
4. Perform exchange steps:
    - A one-point exchange step consists of adding to the current design the point in the candidate list that improves the optimality criterion the most and then deletes from the augmented design the point that improves the selection criterion the least.
    - A two-point exchange step adds two points in sequence, and then deletes two points.

- An n-point exchange step adds and deletes n points.
- Perform 1-point exchange steps until there is no improvement in the design.
- Then perform 2-point exchange steps, and so on until up to 10-point exchange steps show no improvement to the optimality criterion.
- If at any point, there is improvement, start over with 1-point exchanges.

Point exchange is used to restrict the available runs to a specified candidate set.

Response Surface Designs and Methodology (RSM)

The experiments that target optimization are designed with the use of the Response Surface Methodology (RSM). The aim of this methodology is the "mapping" of the response according to the changes in the factors, in order to find the variables or range of variables of the factors that lead to the optimized response (Georgaki et al., 2010). The response surface is usually represented graphically as depicted in the following figure, where the response is plotted against the selected factors. Contour lines are added to the plot representing a particular height of the response surface. Also, contour plots can be constructed independently representing the response levels against the factors.

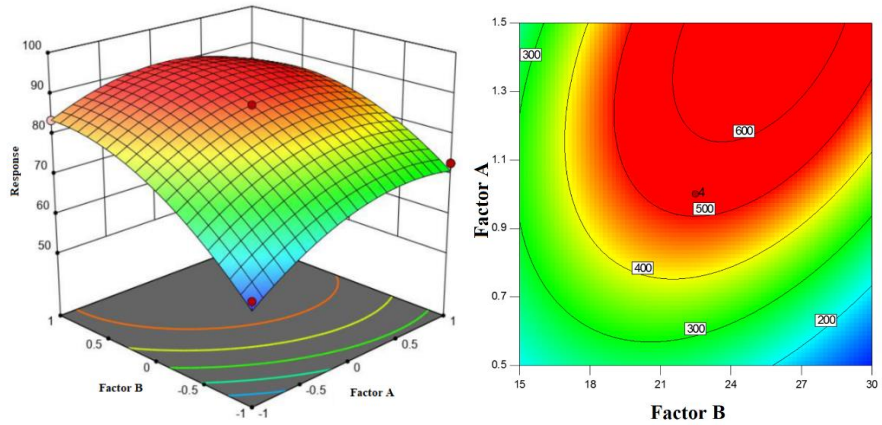


Figure I.2.41: Example of a three-dimensional response surface plot with contour lines (left) and a contour plot (right).

The first step of RSM is to find an approximating functional relationship between the response y and the independent variables. Usually, a low-order polynomial is employed. If the response is well modeled by a linear function of the independent variables, then the approximating function is a fist-order model (Montgomery, 2013):

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k + \varepsilon \qquad \textit{Eq. I.2.19}$$

The orthogonal first-order designs are used for fitting the first-order model, at which, the variance of the regression coefficients is minimized. The 2^k factorial design and the augmented with center points 2^k factorial designs are included in the orthogonal first-order designs. Another orthogonal first-order design is the simplex (Montgomery, 2013).

If there is curvature in the system, then a polynomial of higher order must be used, such as a second-order model (Montgomery, 2013):

$$y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \beta_{ii} {x_i}^2 + \sum_{i<j} \sum \beta_{ij} x_i x_j + \varepsilon \qquad \textit{Eq. I.2.20}$$

The method of least squares is used to estimate the parameters in the approximating polynomials. The response surface analysis is then performed using the fitted surface.

The second-order models can be used for (Montgomery, 2013; Politis, 2010):

- Predicting the response for any factors' variables within the design space
- Determining the level or range of the factors at which the response is optimal

The most used design for fitting a second-order model is the *central composite design (CCD)*. Generally, the CCD consists of a 2^k factorial (or fractional factorial of resolution V) with n_F factorial runs, 2k axial or star runs, and n_C center runs, as shown in the following figure.

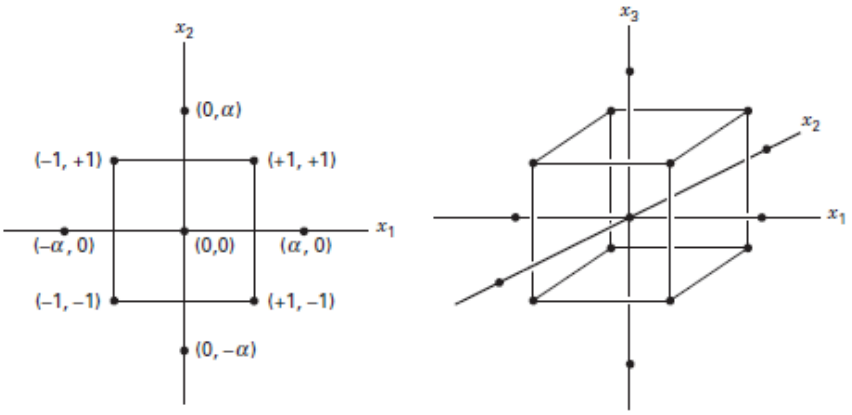


Figure I.2.42: Central Composite Design (CCD) for k=2 (left) and k-3 (right) (Montgomery, 2013).

There are two parameters in the design that must be specified, the distance *a* of the axial runs from the design center and the number of center points n_c. The choice of these parameters depends on the rotatability and the selected center points. Rotatability is important for the second-order model to provide good predictions throughout the region of interest and is a reasonable basis for the selection of a response surface design. As the use of RSM is to find an optimum and since the location of this optimum is unknown prior to running the experiments, it is reasonable to select a design that provides equal precision of estimation in all directions. The choice of *a* makes a CCD rotatable. The value of *a* is calculated by (Montgomery, 2013):

$$a = (n_F)^{1/4} \qquad \textit{Eq. I.2.21}$$

Where, n_F is the number of points used in the factorial portion of the design.

Subcategories of the CCD are (Montgomery, 2013):

- *The spherical CCD*: In this type of designs the rotatability is a spherical property and the region of interest is a sphere. This design puts all the factorial and axial design points on the surface of a sphere of radius $\sqrt{k}$, thus $a = \sqrt{k}$. When the region of interest is a sphere, the design must include center runs to provide reasonably stable variance of the predicted response. Generally, three to five center runs are recommended.
- *Box-Behnken Design*: Three-level designs are used for fitting the response surfaces. These designs are formed by combining 2^k factorials with incomplete block designs. The resulting designs are usually very efficient in terms of the number of required runs, and they are either rotatable or nearly rotatable. Box–Behnken design is a spherical design, with all points lying on a sphere of radius $\sqrt{k}$.

It does not contain any points at the vertices of the cubic region created by the upper and lower limits for each variable.

- *Face-centered central composite design*: At these designs, the region of interest is not spherical but cuboidal and a =1. This design locates the star or axial points on the centers of the faces of the cube. The face-centered cube does not require as many center points as the spherical CCD, however these designs are not rotatable.

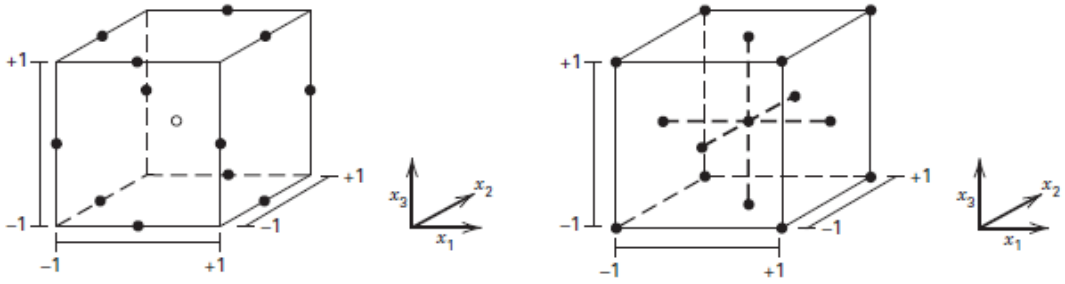


Figure I.2.43: A Box-Behnken design for three factors (left) and a Face-centered central composite design for k=3 (right) (Montgomery, 2013).

- *Other designs:*
  - Another type of CCD design is the *equiradial designs*, in which the points that are equally spaces on a circle and form regular polygons.

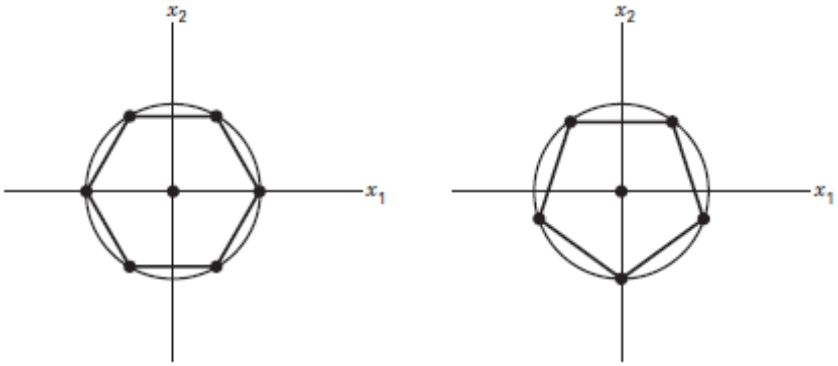


Figure I.2.44: Equiradial designs for two variables. (left) Hexagon, (right) Pentagon (Montgomery, 2013).

  - *The small composite design*: Consists of a fractional factorial design in the cube of resolution III (main effects aliased with two-factor interactions and no two-factor interactions aliased with each other) and the usual axial and center runs. These designs do not have good prediction variance properties in comparison to CCD but are used when it is very important to reduce the number of runs.
  - *Hybrid design*: These designs are also used when it is important to reduce the number of runs, have irregular levels, they are very small designs and have excellent prediction variance properties.

Optimization in multiple responses

In response surface methodology, sometimes it is required to optimize not only a single response, but several responses for specific factors. Thus, it is necessary first to build an appropriate response surface

model for each response and then try to find a set of factors variables that optimize all the responses or at least keeps them in desired ranges (Montgomery, 2013). This is done by either graphical or numerical methods.

In graphical analysis methods, the contour plots of each response are overlayed and visually the appropriate combination of factors (or range of factors) are chosen for the optimal response. This method is a straightforward approach, it works well with few variables, however when there are more than thee design variables, the overlay becomes difficult as the contour plots are two dimensional and the k-2 of the design variables must be held constant to construct the graph. A lot of trial and error is required to either determine the constant factors or what levels to select in order to obtain the best results (Montgomery, 2013).

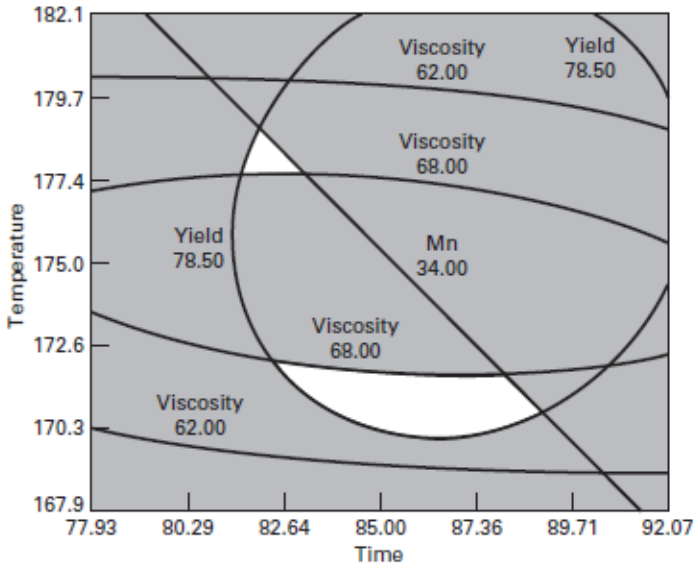


Figure I.2.45: Example of graphical analysis for determining the optimal region for tree design variables (Montgomery, 2013).

A numerical approach often used is the *desirability functions*. In this approach, each response is converted to a desirability function (d_i) that ranges between 0, when the response is outside the acceptable region, and 1, when the response is at its target. Then, the overall desirability (D) is maximized by choosing the desired individual desirability functions. If any of the individual responses is undesirable, then the overall desirability will be zero (Montgomery, 2013).

$$D = (d_1 \cdot d_2 \cdot \ldots \cdot d_m)^{1/m} \qquad \textit{Eq. I.2.22}$$

Where, m are the responses.

This numerical approach is the most used technique, as it is easy to understand and implement, it is independent of the number of responses, weighted responses can be added and is available is almost all software packages (Politis, 2010). An example of the desirability function approach via computer aided analysis is shown in the following figure.

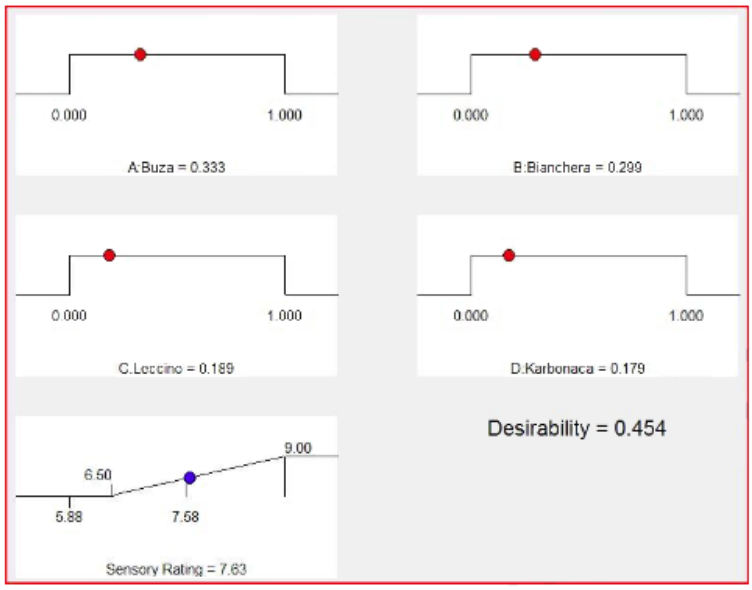


Figure I.2.46: Optimization via desirability functions (Anderson et al., 2018).

Another numerical optimization method is the *steepest ascend or descent or optimal path*. This approach is used when the optimal region of all the responses is not within the initial design space. In this case extrapolation of the design space is needed in order to determine the optimal region. This includes a procedure for moving sequentially in the direction of the maximum increase or the minimization of the response. The direction of steepest ascent is the direction in which increases most rapidly. The actual step size is determined by the experimenter based on process knowledge or other practical considerations. Experiments are conducted along the path of steepest ascent until no further increase in response is observed. Eventually, the experimenter will arrive at the optimal region and additional experiments will be conducted to obtain a more precise estimate of the optimum (Montgomery, 2013).

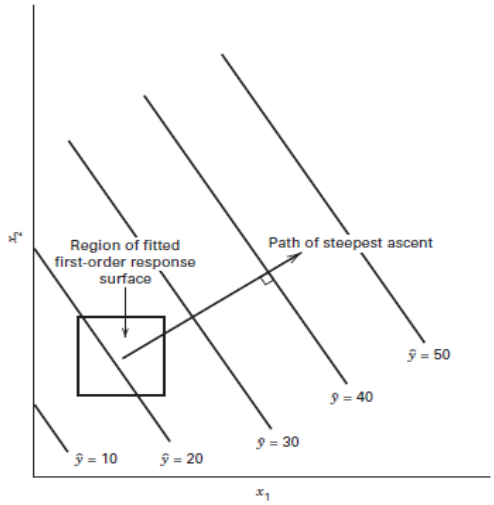


Figure I.2.47: Example of the steepest ascent approach (Montgomery, 2013).

Other less used numerical approaches are the non-linear programming, the dual response method and the sequential simplex method (Politis, 2010).

I.2.6.5. Combination of Mixture-Process designs

This type of designs allows the combination of mixture components and process factors. It is used when it is necessary to simultaneously study the effect of mixture components and process factors. As depicted in Figure I.2.48, this design includes seven blends (triangles) at eight process combinations (cube). Combining each process factor at two levels for all seven blends creates a total of 56 experimental runs.

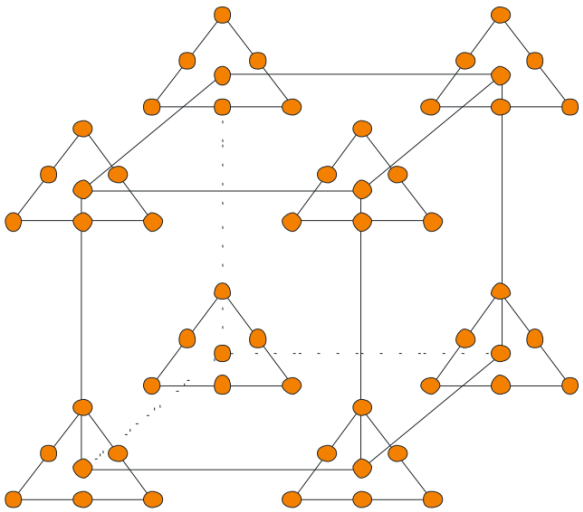


Figure I.2.48: Example of a Mixture-Process design (Stat-Ease Inc., 2021)

The biggest drawback of these designs is the large number of experimental runs; thus, they are not usually used but alternative designs such as optimal (combined) designs are preferred. By using an optimal design, the number of experimental runs for the above example can be decreased down to 29 runs as depicted in the figure below. However, due to random elements in the algorithm, the 29 runs chosen may differ each time an optimal design is performed, but they will be essentially identical in their matrix attributes (Stat-Ease Inc., 2021).

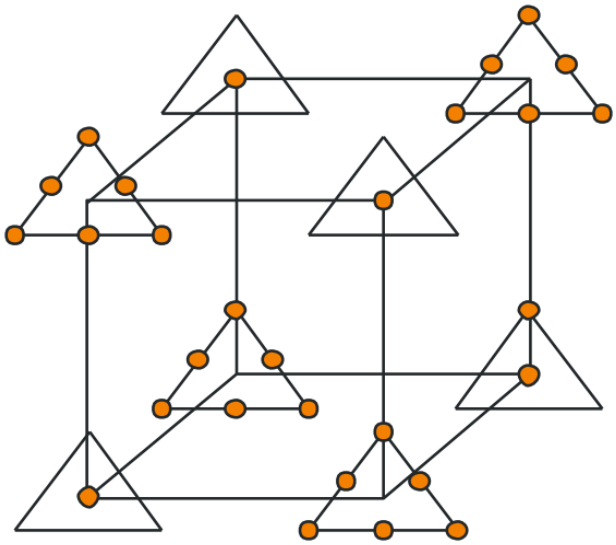


Figure I.2.49: Example of an optimal design (Stat-Ease Inc., 2021).

I.3. PHARMACEUTICAL COMPOUNDING & CUSTOMIZATION

I.3.1. Customization of Pharmaceutical Products

Marketed pharmaceutical products are designed and manufactured in order to address the needs of a broad spectrum of patients and diseases. Almost all developed pharmaceutical forms are placed in the market into a particular dose that fits the average of the population. Characteristics such as age, race, sex, or weight that can lead to variability in the therapeutic effect of the selected dosage form are not taken into consideration when designing a pharmaceutical product. This is more evident in pediatric populations, where the customization of the API dose is essential. Other examples include dosage forms with narrow therapeutic index or APIs that interact with certain foods and commonly used medications or different clinical circumstances in which people with different medical and biological conditions need personalized release profiles. Thus, the "*one-size fits all*" approach is not suitable for all; thus, the field of precision medicine is gaining ground. This allows the individual patient to be prescribed with customized dosages and tailored release profiles of suitable pharmaceutical forms (Tan et al., 2021).

However, the approach of personalized medicine is challenging, complex and costly, leading to limited large-scale applications and expensive pharmaceutical products. A tool such as 3D printing technology can potentially overcome these challenges and be a tool allowing easy, flexible, low cost and rapid modification of the dose and release of the API according to the patient's needs and can offer the desired therapeutic effect, at the point of need and at the time of need. By simply varying basic parameters in the CAD design, product customization can be achieved without the need of complex manufacturing equipment and processes.

I.3.2. Pharmaceutical Compounding

Medicinal products manufactured by the pharmaceutical industry and thus on an industrial scale, must hold a marketing authorization obtained by the regulatory authority after a long inspection and examination of all the quality and clinical aspects, which ensure the safety and efficacy of the product. Only then, the pharmaceutical products can be placed on the market. These medicinal products are manufactured and tested in accordance with good practice procedures, which indicate the correct equipment to use, the method of manufacture as well as the control of both the equipment and the production process so that the final product is efficient and ensures patient safety (Gudeman et al., 2013). There are instructions and controls by the regulatory authorities both for the final products and for the production processes, of the appropriate labeling but also for the disposal of the final product.

In some cases, medicinal products which cover special needs of individual patients are not always authorized or available. Thus, the pharmacists are called to cover this gap and prepare medicinal products in the pharmacy, which may be required due to an individual or medicinal condition of the patient and/or an absence or unavailability of appropriate medicinal products on the market. However, even though pharmacists can legally prepare medicinal products in the pharmacy, the quality of the preparation is based on the pharmacist's professional education, professional license, and licensing of the pharmacy's premises. Furthermore, the preparation of galenic products in pharmacies is not harmonized throughout the European countries or worldwide and falls under the national guidelines and the elaboration of the European or US Pharmacopoeia (Council of Europe, 2016). In contrast to the marketed products, galenic preparations are not tested for their effectiveness, safety, and production method as well as for the validation and cleaning of the equipment or their proper labeling and disposal. Therefore, there are deficiencies in the quality control and assurance of these products.

To set an example, the usual approach to dose reduction for pediatric patients initially involves the grinding of commercially available adult tablets in a mortar. The formed pharmaceutical powders consisting of the active substance and the excipients are then diluted with additional excipients to reduce the dose, mixed and then weighed so that the final mixture contains the desired pediatric dose. This method has significant disadvantages and limitations in relation to the required control procedures to ensure that the patient receives the expected dose.

In other words, the above practice does not guarantee the identity of the additional diluent, the homogeneous distribution of the dose in the final mixture, as these methods are not validated, and no appropriate analytical technique is used to confirm the dose in the final mixture. The possibility of error is obvious, and it is not possible to identify it before the product is administered to the patient. In short, this is a process that in the modern regulatory environment would not be likely to be approved by drug control authorities.

Similar methods are followed in Pharmacies for the preparation of galenic preparations according to relevant medical prescriptions when the same reasons are already mentioned.

From all the above it is obvious that the prevailing approach so far has many serious disadvantages in terms of its application in the production of personalized medicinal products, especially when using pharmacologically active substances in low doses with a narrow therapeutic range in groups of patients such as children.

European and American regulators have recently sought to fill this gap by issuing instructions on the proper manufacture, registration, labeling and disposal of pharmaceutical products produced in pharmacies to reduce the aforementioned risks (Council of Europe, 2016; U.S. Department of Health and Human Servises Food and Drug Administration Center for Drug Evaluaion and Research, 2014; U.S. Food and Drug Administration, 2017).

Emphasizing on this issue, the Council of Europe has adopted a Directive in 2016, "*Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients*" (Council of Europe, 2016), according to which, the product and the manufacturing process must follow specific principles such as commercially available products. For example, all products should be manufactured in a process that ensures the quality of the final product (quality assurance system). This can be done either with appropriate equipment for controls within the process itself (in-process controls) or with controls on the final product. To select the appropriate quality control process, a risk assessment study should be conducted prior to production. In addition, the production

process, the results of the controls, the assured quality of the raw materials and the risk management study should be recorded so that there is transparency and the traceability of the products and the production process is assured (Council of Europe, 2016).

Similarly in 2018, the US Department of Health and Human Services (FDA) issued guidelines for the production of galenic preparations from special facilities suitable for these practices (Compounding Policy Priorities Plan, 2018) (Scott Gottlieb, 2018). As in the European directives, it is necessary to conduct a risk assessment study (Risk-Based Approach to Manufacturing Standards for Outsourcing Facilities) (Palmer, 2018) and the production process should be in accordance with the principles of good practice process (U.S. Food and Drug Administration (FDA), 2018).

According to these recent instructions of the world regulatory authorities and the so far approach for the production of personalized medicines, as well as the principles of Pharma 4.0, there is a need to fill the existing gap in pharmaceutical compounding. A system or an approach which enables the production of personalized medicinal products at the point of need in combination with automated quality controls and quality assurance in real time of both the critical quality characteristics of the final product and the critical parameters of the production process, needs to be developed in order to assure patient safety regardless the production infrastructure.

I.3.3. Healthcare and Medication errors

In addition to the compounding process, which does not assure the effectiveness, safety, and production method of the medicinal products prepared in pharmacies, in the healthcare sector in general, a major concern that needs to be faced is healthcare medication errors. According to the Institute of Medicine in the US (Institute of Medicine (US) Committee on Quality of Health Care in America, 2000), the deaths as a result of healthcare errors, range from 44,000 to 98,000 annually, making healthcare errors the 8th leading cause of death. In fact, more people die each year as a result of healthcare errors compared to motor vehicle accidents, breast cancer or even HIV. Additionally, the Institute of medicine (Roehr, 2006) reports that drug related errors are the most common medical errors and can occur at every stage from prescription through to monitoring the patient's response. It was estimated that on average at least one drug error per hospital patient occurs each day and says that the rate of error varies widely among facilities.

In order to prevent these healthcare errors and particularly the medication errors, the guidance or let's say the standard for safe medication practices which, the health practitioners should follow, is well known as *"The 5 rights"* (Grissinger, 2010). An abbreviation for delivering:

To the right patient

the right drug

at the right dose

through the right route

at the right time

However, the five rights rely too much in human judgment, manage the problem not as a whole but instead in a fragmented way, and thus it has been proved ineffective. As a conclusion, the current practice does not consider that safety in drug delivery to the patients can only be addressed through a systems approach. So,

there is a need to help the practitioners achieve these goals by establishing a novel, reliable system thinking and acting process, which will ensure the correct execution of the safest possible practices as a whole.

In this context and based on the tools of 'Pharma 4.0', a system which reduces healthcare-medication errors and ensures the five rights and thus patient safety can and should become a reality in everyday clinical practice.

I.4 PURPOSE OF THE STUDY

The main objective of the study was to demonstrate the applicability of 3D printing technology in the pharmaceutical field for the production of personalized dosage forms at the point of need and when in need, while assuring product quality. The combination of Pharma 4.0 technologies such as 3D printing and Machine Vision, analytical techniques, and Quality by Design showed that precision medicines can be manufactured on demand and at the same time assuring both quality and traceability during the whole production process.

In more detail, the present study is divided in two main pillars, named "*Partial Tablet Coating by 3D Printing"* and "*A 3D Printing and Machine Vision Application for Quality Risk Management in Compounding Drug Products at the Point of Need*". The first pillar demonstrates how 3D printing technology can be successfully used in addressing the challenging demands for designing dosage forms with release profiles customized to each patient unique needs and/or production at the point of need. More specifically, two model APIs were chosen and formulated as tablets, which were then partially coated by a picked glyceride with 3D Printing. The core tablets were prepared with the conventional direct compression manufacturing process in order to present an alternative application of 3D Printing on how it can be used to already commercially available dosage forms as well in order to alter-customize the release profile of the API according to the desired therapeutic effect. The inter-individual differences in patients (e.g., race, age, weight, disease condition and pharmacokinetic characteristics) lead to variability in the therapeutic effect, even for the same dosage form. Thus, the approach proposed can be applicable for small batches of patient-specific dosage forms at the point of need, e.g., at the Hospital Pharmacy.

The feasibility of employing the 3DP technology for the partial coating of matrix tablets with glycerides, where the API's release would be precisely regulated by controlling the coating characteristics only, without modifying the core formulation is illustrated. This would benefit the production of dosage forms with tailormade release profiles without the need of complex equipment and processes, thus accelerating the time from production to patient and furthermore, producing complex coating geometries that are not able to be created by conventional coating methods. In combination with Design of Experiments, a major tool for the implementation of statistical thinking and Quality by Design in pharmaceutical development, 3D Printing proved a simple and reliable tool for fine-tuning such a Critical Quality Attribute.

Experimental design was used as a statistical tool to characterize the effects and possible interactions of selected parameters of the printing/coating process on the release profiles of the two APIs. The feasibility of the proposed technology was shown by modifying the geometry of the coating and acquiring knowledge on which of these parameters and/or their interactions affect the release profile of the APIs and thus achieving personalized drug release rates according to the patient's needs.

After realizing the possibilities and applications of 3D Printing in combination with the gap that exists in pharmaceutical compounding processes as well as the increased numbers of medication errors, a solution

to assure quality when preparing pharmaceutical products in Community and/or Hospital Pharmacies and thus mitigating the risks associated with healthcare-medication errors, has been developed. Thus, the objective of the second pillar, "*A 3D Printing and Machine Vision Application for Quality Risk Management in Compounding Drug Products at the Point of Need*", was to develop a reliable, flexible, cost-effective and most of all, patient centered system to not only produce the personalized dosage forms, but also assure quality and traceability throughout the whole production process.

The system designed is in line with the most recent regulatory directives incorporating Industry 4.0 key enabling technologies and allows the production of personalized medicinal products at the point of need with the use of 3D Printing, while a combined Deep Neural Network based Machine Vision system and analytical methodology assure both quality and traceability during the whole production process. Thus, the entire supply chain of a personalized drug product, from the raw materials and through its manufacturing process to the patient, is quality assured, recorded and fully traceable through a reliable systems thinking and acting approach.

All the relevant information, such as who the patient is, which drug and dose are required, what raw materials are used, when and how it was produced, or what possibly went wrong during the whole process is fully monitored, filed, and reported, ensuring the "five rights". So, in practice, the patient instead of getting a box of pills with dosage instructions or cutting pills in half to have the right dosage, this system will print the "personalized dosage form" in the amount needed and with all the relevant information recorded and available to the physician.

To demonstrate the feasibility of such a system, orodispersible films were constructed by 3D Printing, where the API's dose was accurately regulated simply by the varying film's size. The automated in-process quality controls for the raw materials, bulk solution, and final films, were carried out by techniques such as UV/Vis, FT-IR, or Raman spectroscopy, coupled with Machine Vision for monitoring, identification and excluding defective films. The identification and quantification of the API was evaluated with one of the previously mentioned analytical techniques. A Deep Neural Network based Machine Vision system was finally developed to categorize the final products into "conforming" and "not conforming", with high accuracy.

This approach could be the basis for the production of small batches and fully customized dosage forms without the need of complex equipment and processes, at the point of need, complying with the quality guidelines and mitigating the patient risks associated with compounding activities.

Both pillars revealed that 3D printing technology could be employed for addressing the challenges associated with personalized medicine, such as complex designs, limited manufacturing capabilities or costly processes. By exploiting the advantages of 3D printing technology such as flexibility, cost effectiveness, robustness, versatility, precision, and speed, new possibilities to product development and manufacturing were possible. In addition, 3D printing as a Pharma 4.0 tool follows the principles of the modern manufacturing approaches such as Lean and Agile manufacturing, making it a simple and reliable tool for product customization. Thus, through this single-step method, the customized dosage form with the desired quality characteristics can be produced quickly and easily without losses and waiting times between different process steps and at the same time assuring product quality through simple quality controls.

This work offers an improved approach for the compounding activities performed in everyday practices for the production of personalized medicinal products. In contrast to the established techniques followed which cannot assure product and process quality and detectability, the developed approach achieved not only the

production of customized dosage forms but also ensured both quality and traceability during the whole production process. Problems during compounding associated with the identity of the raw materials, the methodology followed, lack of analytical techniques or dose uncertainty are overcome with the adaptation of the present system. Through this system is now possible to identify and minimize the possibility of error during the compounding activities, before administering the product to the patient.

3D printing proved an excellent tool for the production of personalized medicinal products with customized release profiles and doses at the point of need and in small size batches. The flexibility, versatility and time saving 3D printing offered in the present project had many serious advantages when compared to the conventional approaches followed. In combination with basic analytical techniques 3D printing has offered an everyday solution in the production of personalized medicinal products at the point of need and when in need.

II. MATERIALS & METHODS

II.1. Materials

II.1.1. Materials used for the Partial Tablet Coating by 3D Printing

II.1.1.1. Tablet formulation

Two APIs, one hydrophilic and one lipophilic, were formulated in two different tablets. The model drugs selected were the hydrophilic methyl-levodopa hydrochloride (Melevodopa, $C_{10}H_{13}NO_4$ HCl) and the lipophilic Acyclovir ($C_8H_{11}N_5O_3$).

Melevodopa is a highly soluble prodrug produced by the esterification of Levodopa used in the clinical treatment of Parkinson's disease and dopamine-responsive dystonia (Bhatia et al., 2017). Absorption of Melevodopa is very sensitive and depends on the state of the stomach and gastrointestinal system.

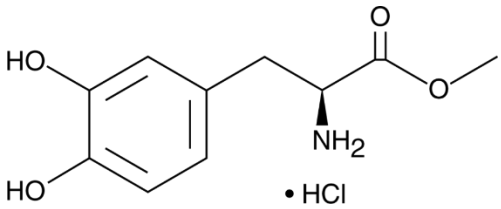


Figure II.1: Methyl-levodopa hydrochloride (Melevodopa) chemical structure.

Acyclovir is an antiviral medication primarily used in the treatment of herpes simplex virus infections, for the acute treatment of herpes zoster, chickenpox, and shingles (Arnal et al., 2008). It can be taken by mouth, applied as a cream, or injected (Wood et al., 1992), is a white, crystalline powder and is slightly soluble in water (Arnal et al., 2008). Acyclovir is a high-risk medicine often administered in pediatric populations; thus, dose adaptation and personalization are required.

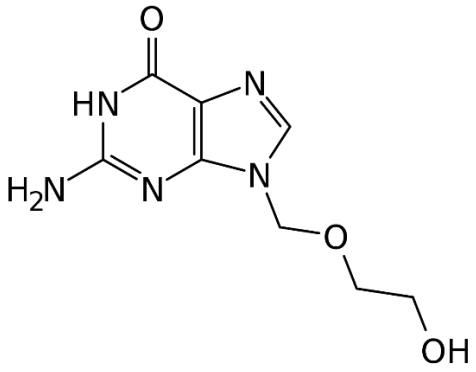


Figure II. 2: Acyclovir chemical structure.

The tablets were formulated according to the composition shown in the following table.

Table II.1: Tablet core formulation (%w/w)

Component	Content	Supplier	Function
Acyclovir or Melevodopa	30%	Fidia S.p.A. (Italy, Lot. 010100) Chiesi Farmaceutici S.p.A. (Italy, Lot. MNTTF004)	Active Pharmaceutical Ingredient
Hypromellose	30%	Methocel E3 Premium LV Colorcon® (UK, Lot. IF10023)	Matrix former
Lactose Monohydrate DC	20%	RetaLac®, Meggle (USA, Lot. L1004A4020)	Filler & Diluent
Microcrystalline Cellulose	19%	Avicel PH-102 ACEF S.p.A. (Italy, Lot. H2622003)	Binder/Diluent
Magnesium Stearate	1%	ACEF S.p.A. (Italy, Lot. C1402005)	Lubricant

II.1.1.2. Coating material

For the coating of the tablets, the glyceride used was glyceryl distearate (Precirol® ATO 5, Gattefossé SAS France, Lot. 161841). It consists of esters of palmitic (C16) and stearic (C18) acids with the diester fraction being predominant. It has a melting range of 50–60 °C and a Hydrophilic-Lipophilic Balance (HLB) of 2 (Gattefosse, 2019). Precirol® ATO 5 functions mainly as a coating agent for protection and taste masking, as a lipid matrix former for modified and sustained release tablets and as a lubricant and flow aid for capsule filling with powders (Ash and Ash, 2007; Gattefosse, 2019). It is also suitable for use in melt processing techniques such as hot melt extrusion, coating, and granulation (Becker et al., 2015; Gattefosse, 2019). Finally, Precirol® ATO 5 has been generally recognized as safe (GRAS) by the FDA and has been used in approved pharmaceutical products (Gattefosse, 2019). The picked glyceride is particularly suitable for partial coating as on one hand it was used in semi-solid extrusion 3DP and on the other hand, it is water insoluble, thus it does not freely permit water penetration through the coating, but only through the uncoated part of the tablet, affecting in this way the release of the API.

II.1.1.3. Dissolution Studies

For the dissolution studies, the following dissolution media were used:

HCl 0.1 N to achieve a pH 1.1

Phosphate buffer (0.3 M Na_2HPO_4) to achieve a final pH 5.5.

II.1.2. Materials used for the 3D Printing and Machine Vision Application for Quality Risk Management in Compounding Drug Products at the Point of Need.

II.1.2.1. Gel & Film Formulation

Warfarin Sodium ($C_{19}H_{15}NaO_4$) was selected as a model drug and formulated in two different sizes of orodispersible films. As a film former, Hypromellose, Methocel™ E4M was used, while water was the main solvent for the gel formation. The composition of the gel is depicted in the following table. Three different %w/w content of Warfarin sodium were used, while the %w/w Hypromellose content was kept stable.

Table II. 2: Gel formulation (%w/w)

Component	Content (%w/w)	Supplier	Function
Warfarin Sodium	2.5%, 5%, 7.5%	Alembic Pharmaceuticals Ltd. (India, Lot. 1804002417)	Active Pharmaceutical Ingredient
Hypromellose	3%	Methocel E4M Colorcon® (UK, Lot.DT302606/00001)	Thickening agent/ film former
Purified Water	q.s. 100%	-	Diluent

Warfarin is a coumarin derivative and is used as an anticoagulant (blood thinner). It is commonly also used to prevent blood clots such as deep vein thrombosis and pulmonary embolism, and to prevent stroke in people who have atrial fibrillation, valvular heart disease or artificial heart valves. It is generally taken by mouth, but may also be used by injection into a vein (Medline Plus, 2017). Warfarin decreases blood clotting by blocking an enzyme called vitamin K epoxide reductase that reactivates vitamin K1. Additionally, because the mechanism involves specific enzymes, patients on warfarin with polymorphisms of these enzymes may require adjustments in therapy, thus requiring lower doses. Thus, warfarin therapy requires dose variability and adjustment according to the patients' individual needs (Dasgupta and Wahed, 2014).

Furthermore, it is known that warfarin interacts with certain foods and commonly used medications. These interactions may enhance or reduce warfarin's anticoagulation effect. Thus, dosing needs adjustments according to these interactions. To optimize the therapeutic effect without risking dangerous side effects such as bleeding, close monitoring of the degree of anticoagulation is required by a blood test measuring such as the International Normalization Ratio (INR) (Dasgupta and Wahed, 2014). When warfarin levels are high, people have more risk of bleeding. Conversely, lower levels of warfarin lead to increased risk of blood clots. There is a narrow range where the benefits of warfarin are greater than the risks, its therapeutic window. Thus, Warfarin is an active ingredient often subjected to the compounding process in order to adjust the dose variations. Warfarin is a white or almost white, hygroscopic, amorphous powder, very soluble in water and in ethanol, soluble in acetone, very slightly soluble in methylene chloride (European Directorate for the Quality of Medicines & Healthcare (EDQM) & Council of Europe, 2019).

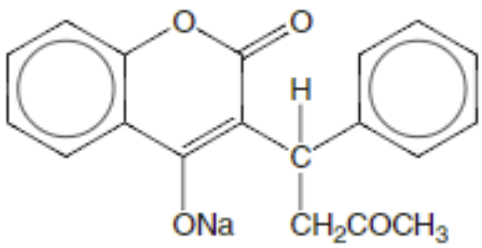


Figure II.3: Warfarin chemical structure (Spiller, 2005)

Methocel™ E4M is a water soluble Hydroxypropyl methyl cellulose (HPMC) polymer with moderate hydroxypropyl substitution and high methoxy content. It is commonly used as a thickener, rheology modifier, binder, film former, and water-retention agent. It is highly soluble both in hot and cold water.

II.2. Methods

II.2.1. Methods & Equipment used in Partial Tablet Coating by 3D Printing

II.2.1.1. Scanning Calorimetry

Scanning Calorimetry (DSC, Mettler Toledo Inc.) was used for the characterization of the glyceride. The DSC measurements were performed in order to identify the alteration of the melting point of the glyceride and thus its polymorphic form upon phase transition. Sealed Aluminum pans with two pin holes were used and a powder aliquot of about 5 mg were firstly heated with a rate of 10 ºC/min from 25 ºC to 85 ºC, under nitrogen purge (100 ml/min), followed by a cooling cycle at the same temperature range and rate. This process was repeated two additional times with the heating rate remaining unchanged but varying the cooling rate. A final heating step was performed at the end of the process. Table 2 shows the cycles' order performed with the corresponding rates and temperature ranges for each sample.

Table II.3: Heating and cooling cycles adopted for the DSC measurements on Precirol® ATO 5 samples.

Cycle	Rate (ºC/min)	Temperature Range (ºC)
Heating 1	10	25-85
Cooling 1	10	85-25
Heating 2	10	25-85
Cooling 2	5	85-25
Heating 3	10	25-85
Cooling 3	1	85-25
Heating 4	10	25-85

II.2.1.2. X-ray Diffraction on Powder

In order to further characterize Precirol® ATO5, untreated and treated glyceride samples were analyzed with X-ray Diffraction on Powder (PXRD, MiniFlex, Rigaku Corporation). The measurements were performed in the angular range of 2-40º (2θ) with a scanning step of 0.05º and generator tube voltage 30 kV. The treated samples were firstly heated in a water bath above their melting point to transit from solid

to liquid. Subsequently, they were left to room temperature, resulting in a rapid solidification. The solid material was turned into fine powder by gentle grinding in a mortar and passed through a 250-micron sieve to obtain homogeneous particles. The untreated material was passed through the same sieve size and finally both samples were analyzed with PXRD.

II.2.1.3. Tableting

The selected formulation presented in Table II.1 was directly compressed into two different 11 mm, flat-faced, round tablets of 280 mg total weight with a single punch tableting machine (Styl'One Evolution, MEDELPHARM SAS, France) using a compression force of 20 kN.

II.2.1.4. 3D printing of partial coating

Tablet coating was carried out using a lab scale 3D printer for semisolids, designed, and constructed at the Dpt. of Mechanical Engineering, University of Parma, Italy. The printer consisted of a rectangular glass printing table and a print head equipped with a 2.5 ml syringe, a G26 needle and a heating system (Figure II.4.A). On top of the printing table, a support structure was printed and attached in order to keep the tablets at the same position while the coating was printed (Figure II.4**Error! Reference source not found.**.B). This support structure consisted of a stable part that was fixed on the printing table and a moving part that was able to slide underneath the stable part. The tablet was inserted between these two parts and with the help of two screws, the moving part encircled the tablet and kept in the same position throughout the printing process. The syringe was loaded with Precirol® ATO 5 powder and was placed in a metal cylinder filled with water, which was constantly heated during the printing process above the material's melting point in order to maintain the glyceride in its liquid form (**Error! Reference source not found.**.C and D). The material was then extruded on the tablet surface by automatically pressing the syringe piston to form the coating in a rectilinear layout and a standard layer height of 0.3 mm according to the CAD. Custom gcode was controlling the initial position of the syringe by setting a new "home" position in order to form the 1st layer of the coating at the correct height on top of the tablet surface.

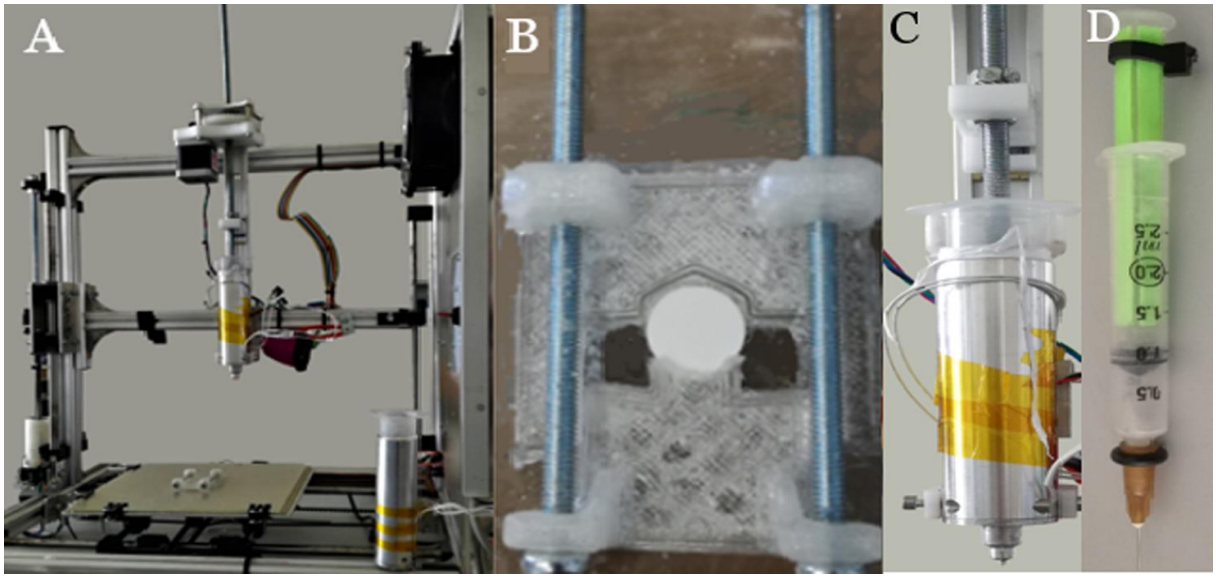


Figure II.4: (A) Semi-solids 3D printer. (B) Tablet support construction attached to the printing table in order to keep the tablet at a constant position. (C) Heating system of the syringe keeping the material in liquid form. (D) 2.5 ml syringe equipped with a G26 needle used for the material extrusion.

II.2.1.5. 3D printing Software

The 3D model of the coating (.stl file) was created with the software OpenSCAD (v.2015-03-2) and the parameters of the 3D printer affecting the coating characteristics (.gcode file) were controlled with the software Slic3r (v.3). The CAD was created by firstly designing a cylinder with a fixed diameter (11.28 mm), the same as the tablet diameter, and by varying only the height. This was expressed in tablet coatings by setting the printing parameters and controlling the extrusion. The main parameters set were the fill pattern (rectilinear) and fill density (25%, 50%, 75% or 100%), the syringe and nozzle diameter (8.66 mm and 0.45 mm respectively), the extruder and bed temperature (60 °C and 50 °C respectively), the extrusion multiplier (set to 1), the 1st and the following layer height (0.3 mm) as well as the print speed (2.1 mm/s) (Appendix, Table A.1).

II.2.1.6. Design of Experiments (DoE)

Two factors at four different levels were chosen to control the coating characteristics, namely Surface Coverage (Factor A) and its Thickness (Factor B). Factor A describes the percentage of the tablet surface covered by the coating, meaning how densely or sparsely the tablet surface is covered by the coating material, while factor B expresses the number of coating layers printed on top of the tablet. For each factor and level, the tablets were coated either on one or both sides, while the lateral surface was always left uncoated. Table II.4 shows the combination of factors and levels chosen, while examples of the CAD drawings of the coatings are shown in Figure II.5**Error! Reference source not found.**. A custom design (Design-Expert® v.11, Stat-Ease Minneapolis, USA) was employed using all possible combinations of the two numeric factors, at the four levels chosen, allowing for the estimation of the main effects and factor interactions. For each API, two different designs were performed, corresponding to the one and the two-sided coated tablets. The Mean Dissolution Time (MDT) (Podczeck, 1993) was chosen as the response factor and each experiment was performed in triplicate.

Table II.4: Factors and Levels of the experimental design for each coated tablet side and each API.

Factor	**Units**	**Level**				**Response**
A (Surface Coverage)	%	25	50	75	100	MDT (min)
B (Thickness)	No. Layers	2	4	6	8	

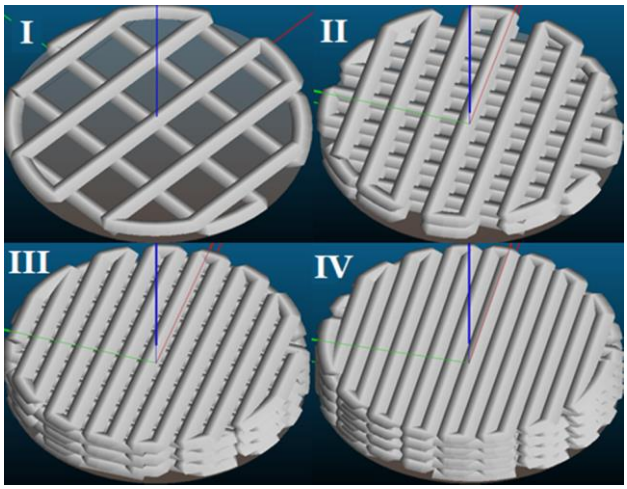


Figure II.5: CAD drawings of coating with the levels of factors A and B increasing from I to IV. (I) Factor A was set at 25% and factor B at two layers. (II) Factor A was set at 50% and factor B at four layers. (III) Factor A was set at 75% and factor B at six layers. (IV) Factor A was set at 100% and factor B at eight layers.

II.2.1.7. Dissolution studies

Dissolution studies were performed for the uncoated and coated tablets in two different media. Initially, 750 ml of HCl 0.1 N at pH 1.1 was used for 1 h followed by the addition of 250 ml phosphate buffer (0.3 M Na_2HPO_4) to achieve a final pH 5.5 and volume of 1000 ml. The dissolution system used (Varian 705 DS, Varian Inc., California, USA) was equipped with an automated sampling pump (IPC, Ismatec®, Cole-Parmer GmbH, Wertheim, Germany) and a UV/Vis spectrophotometer (PerkinElmer Co., Waltham, Massachusetts, USA). Baskets with rotation speed of 100 rpm were used and the samples solutions of Acyclovir and Melevodopa were measured at 256 nm and 280 nm respectively. For comparison purposes the data were expressed with MDT, which can be calculated according to the following equation (Podczeck, 1993):

$$MDT = ABC/M_0 \qquad \textit{Eq. II.1}$$

Where M_0 is the asymptote of the amount of drug dissolved and ABC is the area between the dissolution curve and M_0 can be calculated according to the following equation:

$$ABC = \sum_{i=1}^{n-1} ABC_i = \sum_{i=1}^{n-1} [(t_{i+1} + t_i) \cdot (M_{i+1} - M_i)/2] \qquad \textit{Eq. II.2}$$

where i is the sample number, n is the number of dissolution sample times, M is the amount of drug dissolved at the corresponding sample time.

II.2.1.8. Kinetic model

In order to identify any possible changes in the drug release kinetics when applying the partial glyceride coating to the different APIs, the Korsmeyer-Peppas equation was applied (Korsmeyer et al., 1983):

$$\frac{M_t}{M_0} = k \cdot t^n \qquad \textit{Eq. II.3}$$

where M_t is the amount of drug released at time t, M_0 is the total mass of drug loaded into the device, t is the release time, k is the release rate constant, and n is the diffusional exponent characteristic of the release mechanism.

This equation is only valid for the first 60% of the fractional release and the values expressed by the n exponent represent the release kinetics. In particular, if $n \leq 0.5$ then a Fickian diffusion mechanism occurs, if $0.5 < n < 1.0$ an anomalous (non-Fickian) transport, if $n=1.0$ a Case II (relaxational) transport and if $n > 1.0$ a super case II transport (Dash et al., 2010; Korsmeyer et al., 1983; Vlachou et al., 2017).

II.2.1.9. Statistical analysis

For all the performed experiments, the obtained results are expressed as mean ± standard deviation of three replications. The design space was constructed and analyzed using the Design-Expert® Software, v.11 (Stat-Ease Minneapolis, USA).

II.2.2. Methods & Equipment used for the 3D Printing and Machine Vision Application for Quality Risk Management in Compounding Drug Products at the Point of Need.

II.2.2.1. Gel preparation

The Hypromellose gels were prepared by the "hot/cold" technique as proposed by Colorcon®, meaning 1/3 of the water quantity is heated to ~90°C and Methocel™ powder is dispersed by mixing thoroughly until all particles are wetted, around 30 min. Subsequently, the remaining quantity of water is cooled down to ~10°C and added to the dispersion. The agitation continued for 30 min until both complete solubilization of Methocel™ and the gel reached ambient temperature. Warfarin Sodium was added to the desired gel quantity in order to achieve the %w/w content (2.5%, 5.0% or 7.5% w/w). The 3% w/w content of Hypromellose was chosen as the gel should have enough viscosity in order to both be able to be extruded from the syringe and to form a defined square shape without being misshaped.

II.2.2.2. Film preparation

The formulated gel which varied in %w/w content of Warfarin sodium (2.5%, 5% and 7.5%) was printed in square films of two different sizes, 25x25mm and 15x15mm and thus the final dose varied in the printed films. The 3D printed wet films were then left to ambient temperature for one day in order to dry until stable weight and thus water content and form the orodispersible films. The dry films were then characterized in terms of appearance and shape, dimensions, weight, thickness and %assay. Examples of wet and dry films are shown in Figure II.6. For demonstration purposes, in the formulation, red color was added.

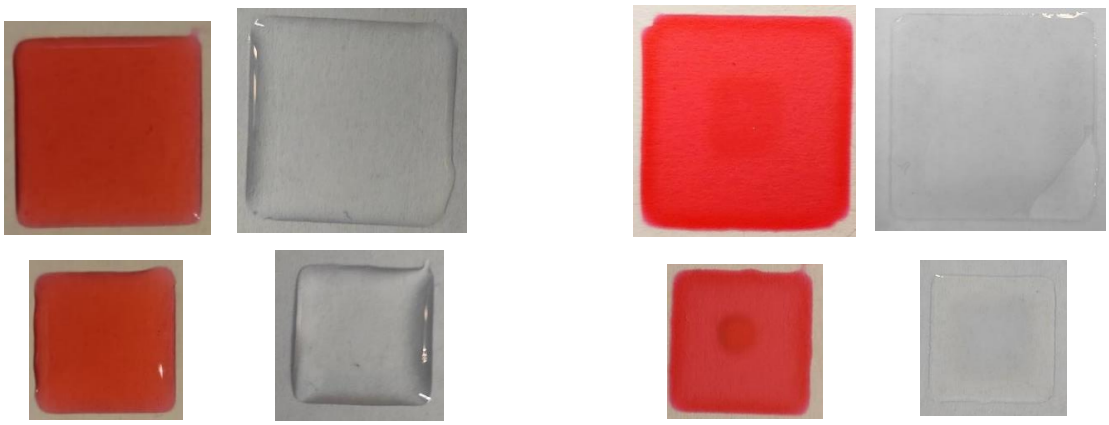


Figure II.6: Examples of wet (left) and dry (right) 3D printed orodispersible films. For demonstration purposes red color was added in the film formulation.

II.2.2.3. 3D printing of orodispersible films

The printing of the orodispersible films was carried out using a commercial 3D printer, Zmorph SX 2.0 (Zmorph SA, Poland). This particular 3D printer is equipped with various interchangeable printing heads as depicted in Figure II.7. Among them, the semisolids print-head, which was used for the printing of the orodispersible films and the FDM dual pro print-head was used for the printing of several adaptors adjusted to the semisolids print-head.

Figure II.7: Zmorph SX 2.0 3D printer (Zmorph, 2022).

The semisolids print-head commercially consists of a 100ml syringe, a piston, and a support base both suitable for this syringe. Finally, a syringe plastic tip instead of a needle is adjusted to the end side of the syringe. The configuration of the semisolids print-head is depicted in Figure II.8. However, the size of the syringe and the syringe tip were not suitable for the printing of detailed film shapes and additionally were not suitable for low quantities of material needed for the creation of the films. In the present design, the use of the 100 ml syringe even after the fine tuning of the printing parameters did not lead to the print of detailed and fine films. For this reason, the use of an alternative syringe of lower capacity and a needle were more appropriate for the creation of the orodispersible films. Thus, the FDM dual pro print-head was used for the fast and easy manufacture of suitable adaptors to adjust a different syringe at the Semisolids print-head. The configuration of the Semisolids and FDM print-heads are depicted in Figure II.8.

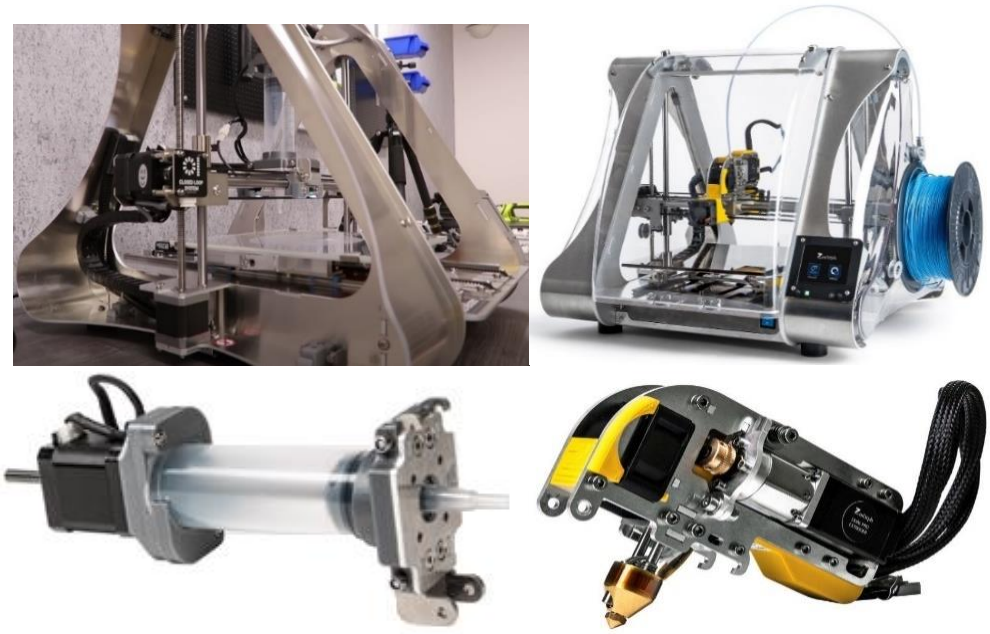


Figure II.8: (Left top and bottom) Semisolids print-head and (Right top and bottom) FDM dual pro pint-head commercial configurations (Zmorph, 2022).

A support base, an adaptor, and a piston, for the adjustment of a 10.0 ml syringe and a needle were designed and printed as depicted in Figure II.9. The printing material used was PLA. These parts replaced the respective default parts used for the support of the 100 ml syringe.

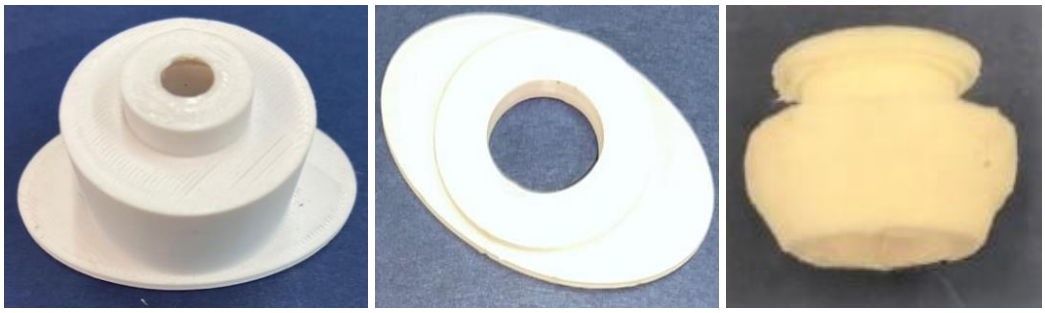


Figure II.9: 3D printed parts of 10.0 ml syringe adaptors.(Left) support base, (middle) adaptor and (right) piston.

Finally, for the creation of the 3D printed films, the printer consisted of a rectangular glass printing table and a Semisolids print head equipped with a 10.0 ml syringe with a G26, which were able to be adjusted due to the printed adaptors (Figure II.10). The syringe was loaded with around 8.0 ml of gel and the material was then extruded on the printing surface by automatically pressing the syringe piston to form the film according to the CAD. Due to the use of a different size of syringe, all printing parameters had to be adjusted differently than the default ones, so the extrusion of the material is within acceptable range regarding first of all the shape and size of the film.

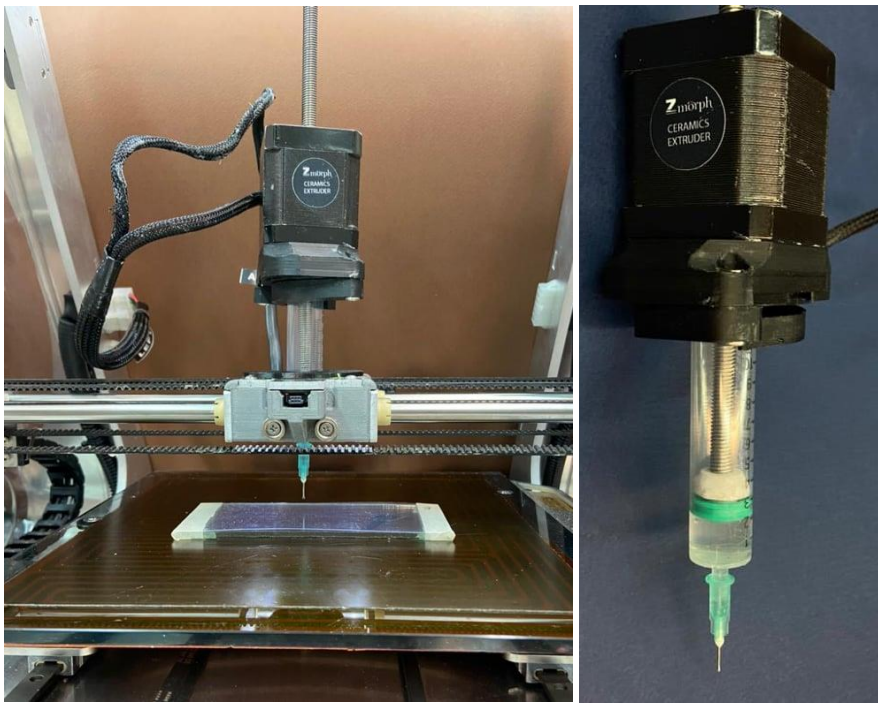


Figure II.10: (Left) Semi-solids 3D printer adjusted configuration, (right) 10.0 ml syringe equipped with a G26 needle used for the material extrusion.

II.2.2.4. 3D printing Software

OpenSCAD software (v.2015.03-2), was utilized for the creation of the digital designs of the adaptor parts needed for the semisolids print-head. The CAD designs are depicted in Figure II.11. Details of the CAD designs and the printing parameters are shown in the Appendix, Figure A.2 to Figure A.4 and Table A.2.

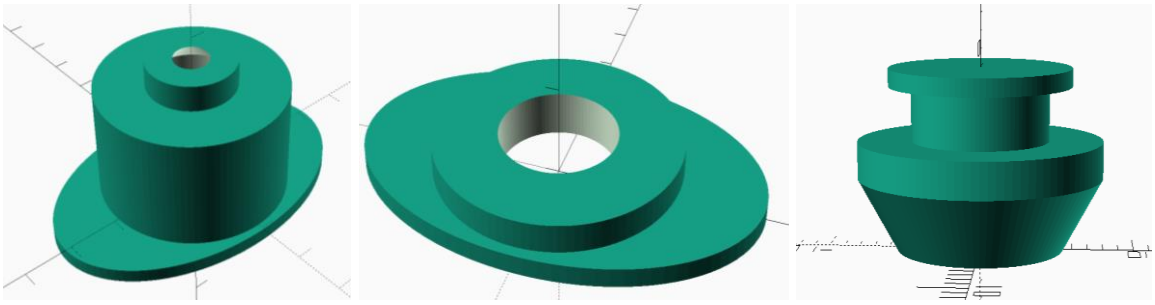


Figure II.11: 3D designs and 3D printed parts of 10.0 ml syringe adaptors.(Left) support base, (middle) top support and (right) piston.

In principle, the creation of a 3D model with the use of the semisolids print-head is performed by controlling the amount of extruded material through the movement of the piston and the movement of the print-head in the xy axis. The object acquires the 3rd dimension by adding layers in the z-axis. Thus, in order to create the digital model of the film, a 2D model (.dxf file) was created with the software OpenSCAD (v.2015-03-2) and the parameters of 3D printer affecting the film characteristics (.gcode file) were controlled with the software Voxelizer v.1.4.18 (ZMorph S.A., Poland). The CAD was created by designing squares one inside the other with a fixed width perimeter. This was expressed in a square film by setting the printing parameters and controlling the extrusion (Figure II.12). The main parameters set were the filament diameter (5 mm)

representing the syringe diameter and the path width (3mm), a parameter expressing the nozzle diameter (syringe needle diameter) but also depends on the material thickness, the layer height (0.1mm) and the layer count (set to 2) as well as the print and travel speed (12 mm/s and 120 mm/s respectively) and finally the retraction was turned off (Appendix,

Table A.3).

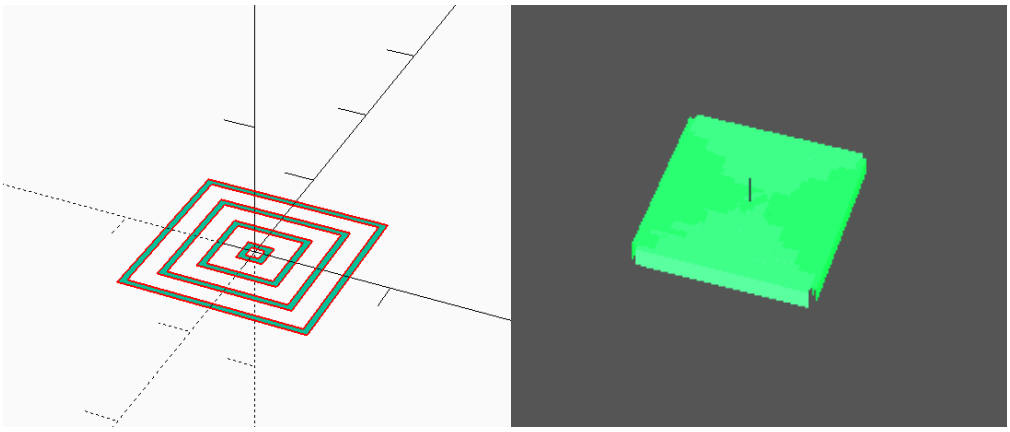


Figure II.12: (Left) CAD drawing and (right) gcode display of the orodispersible film.

II.2.2.5. Characterization of raw materials & films

The raw materials, the gel formulation as well as the orodispersible films were characterized with three different analytical methods, namely UV/Vis spectrophotometry, FT-IR and Raman. The main focus of choosing such technologies was to be cost effective, easy to use, compact and portable so that they could be easily implemented in the quality control system of a hospital or pharmacy setting.

- UV/Vis spectrophotometry

For the UV/Vis measurements, a double beam UV/Vis spectrophotometer (T90+ Double Beam UV Visible Spectrophotometer, PG Instruments Ltd, UK) and quartz glass cuvettes, type 6030, 10 mm (Hellma®, USA) were used. The active ingredient Warfarin sodium was dissolved in water and scanned in the wavelength range of 190-800 nm in order to find the Lmax, which proved to be at 308 nm. Placebo gels and films were also tested in order to verify that none of the other components of the formulation absorbed at this wavelength.

- FT-IR spectroscopy

IR measurements were performed with a diamond ATR with pathlength 1.2 μm at 1700 cm^{-1} and a level of detection LOD ~1% (Cary 630FTIR, Agilent Technologies Inc., California, USA). Each material of the formulation was scanned at the wavenumber range of 650-4000 cm^{-1} in order to identify the characteristic bands of each component.

- Rama spectroscopy

For Raman spectroscopy, the instrument was adjusted to standard exposure, high intensity and used a nozzle of 1.5mm (Serstech 100 Indicator, Serstech AB, Sweden). Each material of the formulation was scanned at the wavenumber range of 400-2300 cm^{-1} in order to identify the characteristic bands of each component.

- Finally, images of solid Warfarin sodium and Hypromellose using a stereoscope (Olympus SC30, Japan) and a polarized microscope (Olympus BX41, Japan) in order to verify their amorphous or crystalline form.

II.2.2.6. Machine vision

A Deep Neural Network based Machine Vision system was developed to identify potentially defected films ("conforming" and "not conforming") and classify them into four different categories, defined as "Conforming", "Type I Defect", "Type II Defect" and "Type III Defect". This was possible by transfer learning of the already developed neural network GoogleNet, a type of convolutional neural network based on the inception architecture (Szegedy et al., 2014). Matlab R2022a was used in order to modify the neural network according to the needs of the film categorization. This simplified the neural training as a significant amount of time was saved (minutes instead of hours), the sets of training data were far less (dozens instead of thousands), and a simple PC was used instead of clusters. The final layers of the GoogLeNet were modified in order to reform the output of the network to match the four film categories and the data set was expressed as imageDatastore (Figure II.13). Data augmentation was used to increase the data set. 70% of the data set was used to train the network while the 30% was used for the network validation. A new, unknown set of data was used for the testing of the network. Finally, the neural was trained using the stochastic gradient descent with momentum (SGDM) method.

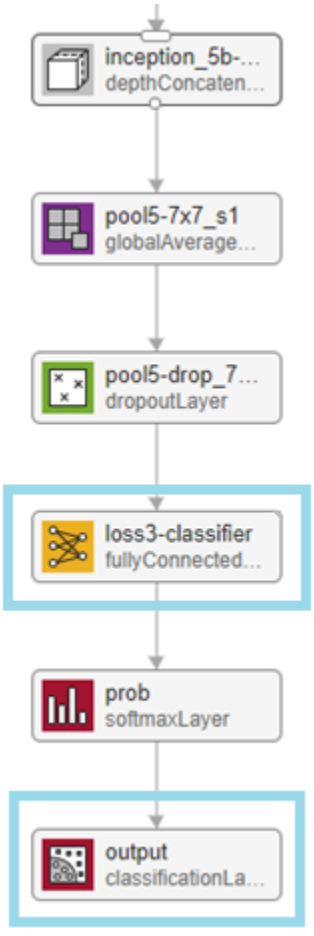


Figure II.13: Final GoogLeNet neural network layers. In blue boxes are the layers that were changed in order to modify the network according to the needs of the film categorization.

The hyperparameters set were the following:

Learning rate (0.01 - 0.0001): controls how much to change the model in response to the estimated error each time the model weights are updated. A value too small may result in a long training process that could get stuck, whereas a value too large may result in learning a sub-optimal set of weights too fast or an unstable training process.

(Mini)Batch Size: splits the training dataset into small batches that are used to calculate model error and update model coefficients. Small values give a learning process that converges quickly at the cost of noise in the training process, while large values give a learning process that converges slowly with accurate estimates of the error gradient.

Max Epochs (5-20): Defines the number of times that the learning algorithm will work through the entire training dataset. One epoch means that each sample in the training dataset has had an opportunity to update the internal model parameters. An epoch is comprised of one or more batches.

III. RESULTS & DISCUSSION

III.1. Partial Tablet Coating by 3D Printing

III.1.1. Characterization of coating material

Precirol® ATO5 is a commercial product constituting of a mixture of esters of palmitic (C_{16}) and stearic (C_{18}) acids. It has been reported that lipid molecules show different three-dimensional structures: unstable α form with the lowest melting temperature, metastable β′, and the most stable the β modification. For mixtures of glycerides, additional intermediate βi forms, between β′ and β exist (Araújo et al., 2010). The results of the DSC measurements are shown in Table III.1 and Figure III.1. Precirol® ATO5 is characterized by quite a complex melting behavior as it melts over a relatively wide range of temperatures.

Table III.1: DSC parameters recorded with Precirol® ATO5 at different heating or cooling cycles.

Cycle	Onset temperature (°C)	Peak temperature (°C)	ΔE (J/g)
Heating 1	57.5	65.2	-210.12
Heating 2	53.83	60.84	-144.96
Heating 3	53.17	60.86	-148.96
Heating 4	50.99	60.91	-157.44
Cooling 1	57.76	56.29	142.75
Cooling 2	58.34	57.06	160.36
Cooling 3	59.17	57.95	133.76

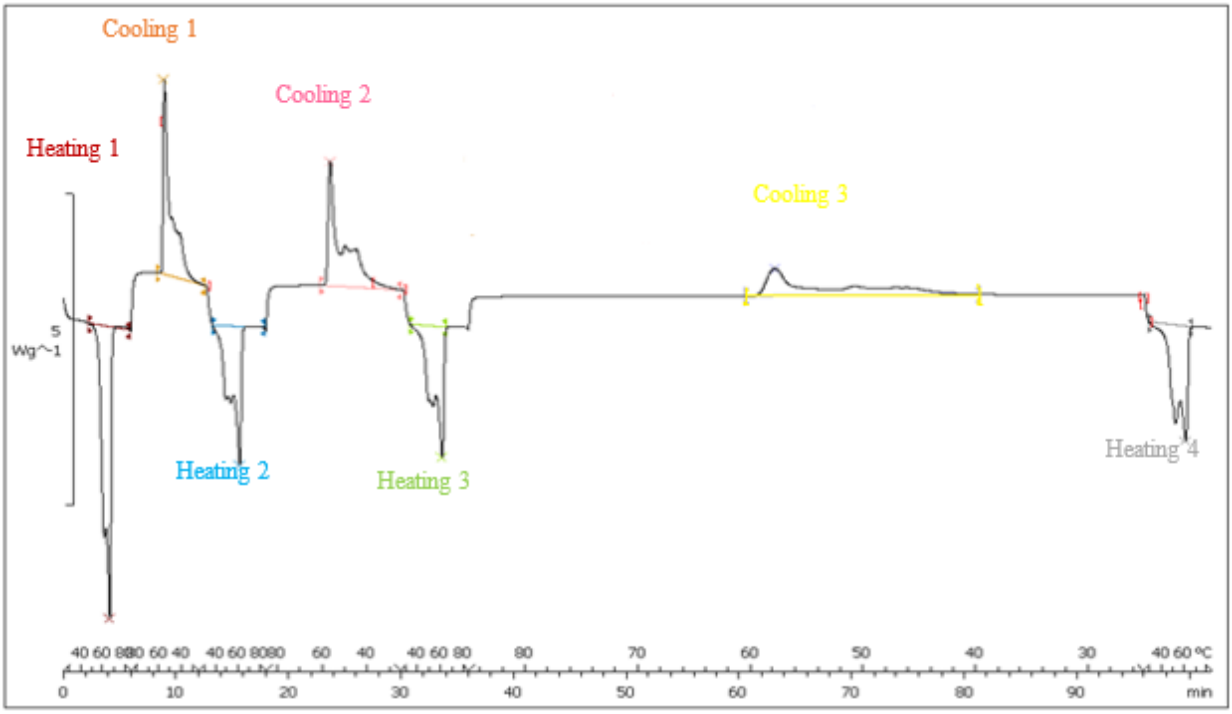


Figure III.1: DSC traces of Precirol® ATO 5 obtained with heating or cooling cycles. Red: Cycle Heating 1, Orange: Cycle Cooling 1, Blue: Cycle Heating 2, Pink: Cycle Cooling 2, Green: Cycle Heating 3, Yellow: Cycle Cooling 3, Grey: Cycle Heating 4.

The DSC curves obtained exhibit a sharp endothermic event ascribing to the melting at 65.2 °C with an onset at 57.5 °C and a small left shoulder of lower enthalpy. The main curve probably is due to the stable β form, while the shoulder might be the metastable α polymorphic form (Kasongo et al., 2011) as the less stable α form melts at lower temperatures than β form (Doktorovová et al., 2010). Since the diester fraction of the glyceride is predominating, the main modification in which the Precirol® crystallizes should be the β′ or β form (Hagemann and Rothfus, 1993). Performing a second heating step at the crystalized Precirol®, the melting peak shifts at 60.8°C with an onset of 53.8°C, resulting probably to a different polymorphic form. As the material is a mixture of two types of triglycerides with different chain length, occurrence of intermediate β_i forms is possible (Doktorovová et al., 2010). Additional heating after cooling in different rates, does not show any shift at the melting peak of Precirol® ATO5, indicating probably no further change in the polymorphic form.

In order to verify the change of polymorphic form of the glyceride after melting and re-solidification, PXRD measurements were performed to untreated and treated material. The results of the analysis are shown in Figure III.2.

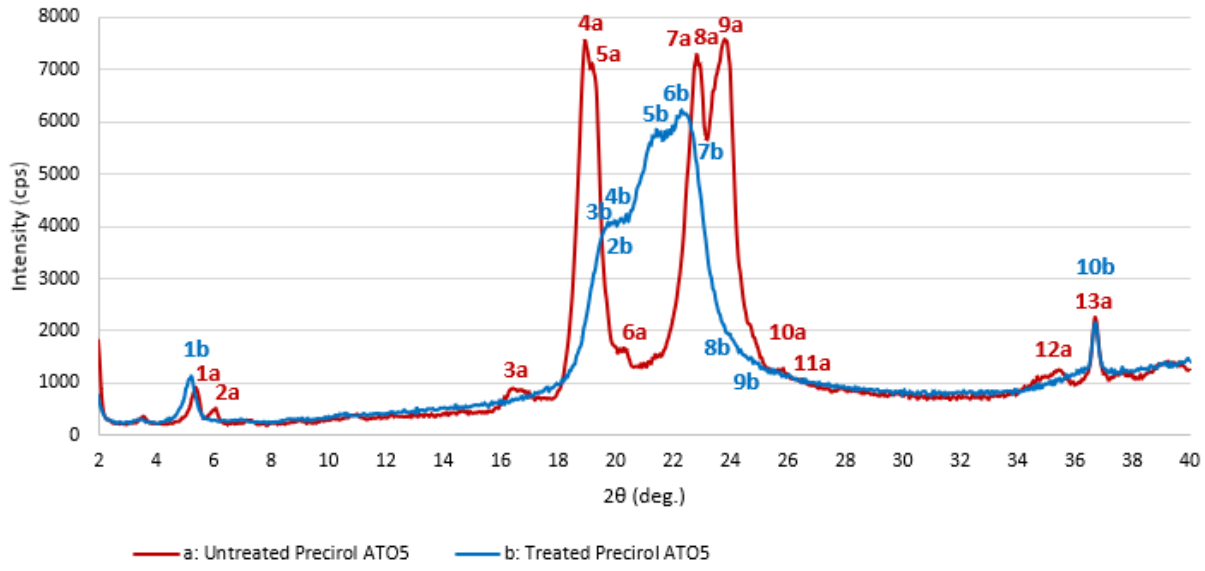


Figure III.2: PXRD patterns of Precirol® ATO5. Blue line and subscript (a) refer to the untreated material, while red line and subscript (b) to treated material.

The results of the XRD analysis reported in Figure III.2 show a change in the polymorphic form of Precirol® ATO5 between the raw-untreated material and the treated material. Prior to heating, Precirol ATO5 shows four main peaks at 18.95, 22.85, 23.45 and 23.90 deg., while the powder recrystallized from the melt showed a cluster of peaks between 19.30 and 24.90 deg. Exposing the material to a temperature above its melting point alters the degree of crystallinity and the polymorphic nature of the solid lipid obtained upon re-solidification (Kasongo et al., 2011).

According to Doktorovová et al. (Doktorovová et al., 2010), in bulk Precirol ATO5 four reflectons were observed at 19.37, 22.84, 23.01 and 23.19 deg., which could reflect the presence of various β_i forms, as might be created in mixtures of glycerides with different fatty acid residue composition. Hamdani et al., observed a single peak at 21.5 deg. of recrystallized Precirol ATO5 corresponding to a change in the polymorphic form of the lipid from β to α-modification (Hamdani et al., 2003).

These observations are consistent with the DSC traces and PXRD patterns generated in this work. Therefore, it can be assumed that Precirol ATO 5 exists mainly in the crystalline β-modification prior to heating and upon heating it crystallizes in the α-modification. These forms differ in stability or their physicochemical properties such as melting point, recrystallization rate and solubility in water. Thus, this change of polymorphic form might impact the physical stability or dissolution rate of the final formulation (Becker et al., 2015).

III.1.2. Experimental Design

The hydrophilic Melevodopa and the lipophilic Acyclovir tablets were partially coated with the glyceride Precirol ATO5 using the semi-solids 3D printer according to the experimental design. Subsequently, the dissolution profiles were recorded and analyzed in order to identify the effect and/or interactions of the selected coating parameters on the API release according to the design matrices. Examples of the actual partially coated tablets are shown in Figure III.3.

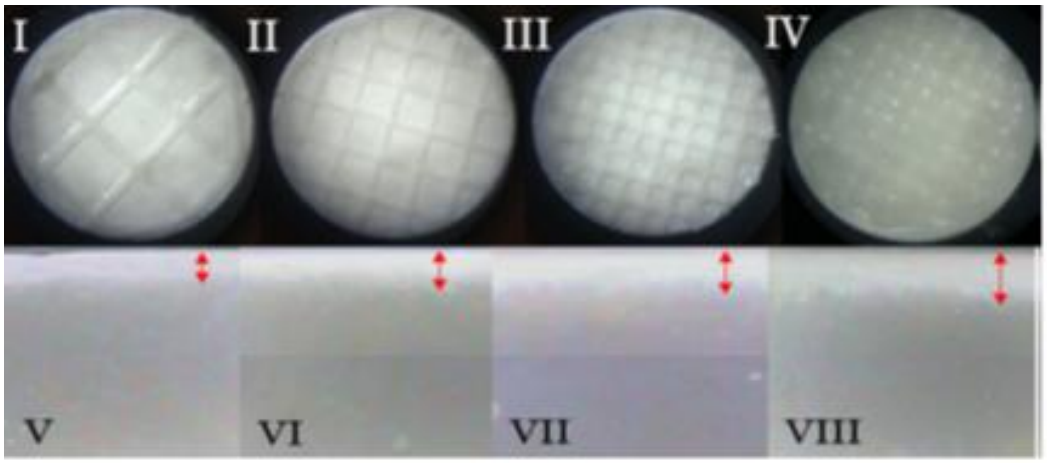


Figure III.3: Examples of partially coated tablets with 3DP with the four levels of factor A and B. (I) top perspective - A:25%, (II) top perspective - A:50%, (III) top perspective - A:75%, (IV) top perspective - A:100%, (V) side perspective - B:2 layers, (VI) side perspective - B:4 layers, (VII) side perspective - B:6 layers and (VIII) side perspective - B:8 layers (Microscopes: Zeiss Jena Citoval 2 and Leica Microsystems, Q500IW). The red arrows indicate the coating thickness.

Uncoated tablets

Firstly, the uncoated core tablets of both APIs were tested at the same dissolution conditions and the dissolution parameters expressed in terms of MDT are shown Table III.2.

Table III.2: MDT of uncoated-core Melevodopa and Acyclovir tablets.

API	MDT (min)
Melevodopa	65.50 ± 1.64
Acyclovir	112.67 ± 6.11

Both types of tablets can be regarded as swellable matrix tablets, at which a gel layer forms around the matrix (**Error! Reference source not found.**Figure III.4, I). Since the tablet formulation of both APIs consists of the same excipients, the release is considered dependent on the drug diffusion through the gel layer and dissolution of the API in the medium. As expected, the hydrophilic API Melevodopa showed a faster release, as depicted by its lower MDT compared to the lipophilic compound as well as its release profile (Figure III.5). At 60 min and 120 min more than 50% and 85% of the active substance was released respectively, while until 300 min the tablet had fully dissolved (Figure III.4,II). Acyclovir due to its poorer solubility exhibited a slower release profile (Figure III.5). At 60 min, 35% of the active substance was released, at 120 min 50%, while at 300 min 85%. At the end of the dissolution process, the swelling of the Acyclovir matrix tablet was obvious, but the tablet had not dissolved completely (Figure III.4, III).

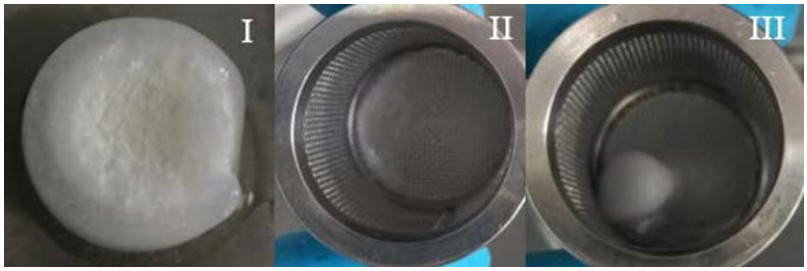


Figure III.4: (I) Gel layer forming around the matrix, (II) Melevodopa uncoated tablet completely dissolved after the end of the dissolution (III) Acyclovir uncoated tablet after the end of dissolution.

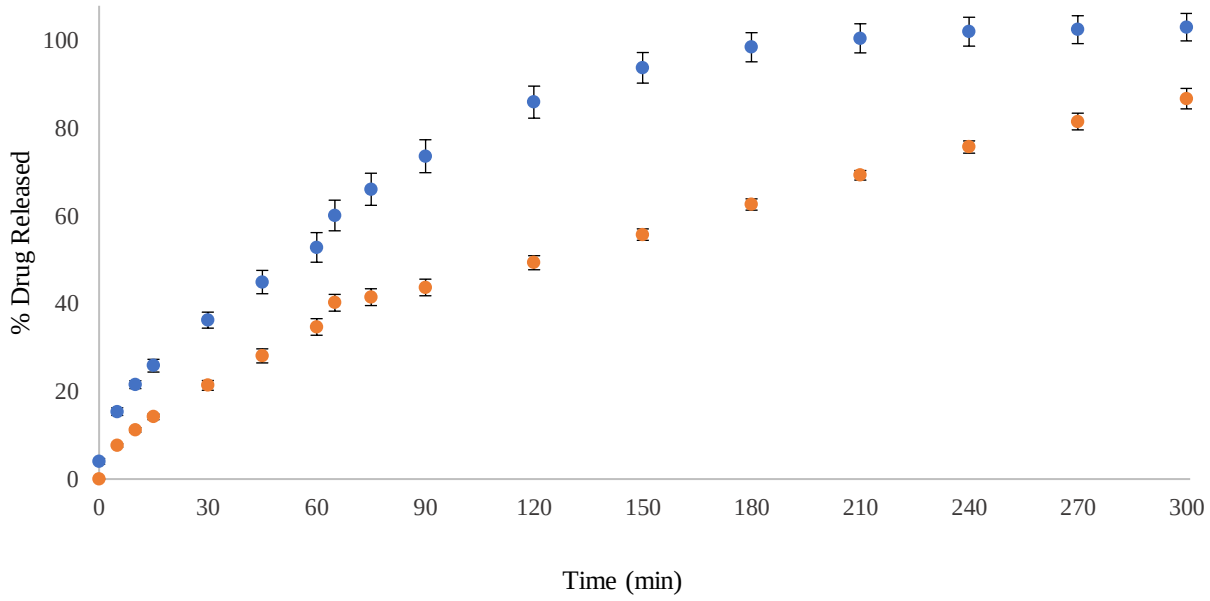


Figure III.5: Dissolution profiles of the uncoated tablets. Blue circle: Melevodopa uncoated tablets, orange circle: Acyclovir uncoated tablets.

Design I: Melevodopa one-side coated tablets

The first experimental design performed was for the hydrophilic API, Melevodopa, for a tablet coated on one side only. 16 runs with different combinations of factor A and B at four levels were performed as shown in Table III.3.

Table III.3: Experimental design for Melevodopa tablets coated on one side.

Run	Factor A: Surface Coverage (%)	Factor B: Thickness (No. Layers)	Response: MDT (min)
1	25	4	63.39 ± 1.27
2	50	8	65.71 ± 1.75
3	75	6	84.79 ± 4.27
4	100	6	94.87 ± 3.55
5	25	8	69.23 ± 1.89
6	50	2	67.94 ± 3.56
7	75	8	89.12 ± 6.07
8	25	2	65.11 ± 1.27
9	50	6	81.42 ± 5.92
10	75	2	71.29 ± 7.48
11	75	4	79.10 ± 8.28
12	25	6	70.73 ± 1.79
13	50	4	75.71 ± 3.36
14	100	8	89.89 ± 3.67
15	100	4	84.90 ± 3.14
16	100	2	68.04 ± 9.33

The statistical analysis showed that the factors A and B were significant ($p < 0.05$), while their interaction AB was marginally not significant. The results are depicted in detail in Figure III.6. Not surprisingly, the increase of factors A and B resulted in an increased MDT. Regarding the AB interaction, the effect of factor B on MDT is more pronounced when factor A is at its highest level. This means that the effect of the number of layers on the selected response is more pronounced when the surface coverage is higher. The equation describing this relationship is as follows:

$$MDT = +76.33 + 9.05 \cdot A + 5.75 \cdot B + 4.12 \cdot AB \qquad \textit{Eq. III.1}$$

where MDT is expressed in min, A: Surface Coverage, B: Thickness and $-1 < A, B < 1$. The high levels of the factors are coded as +1 and the low levels are coded as −1.

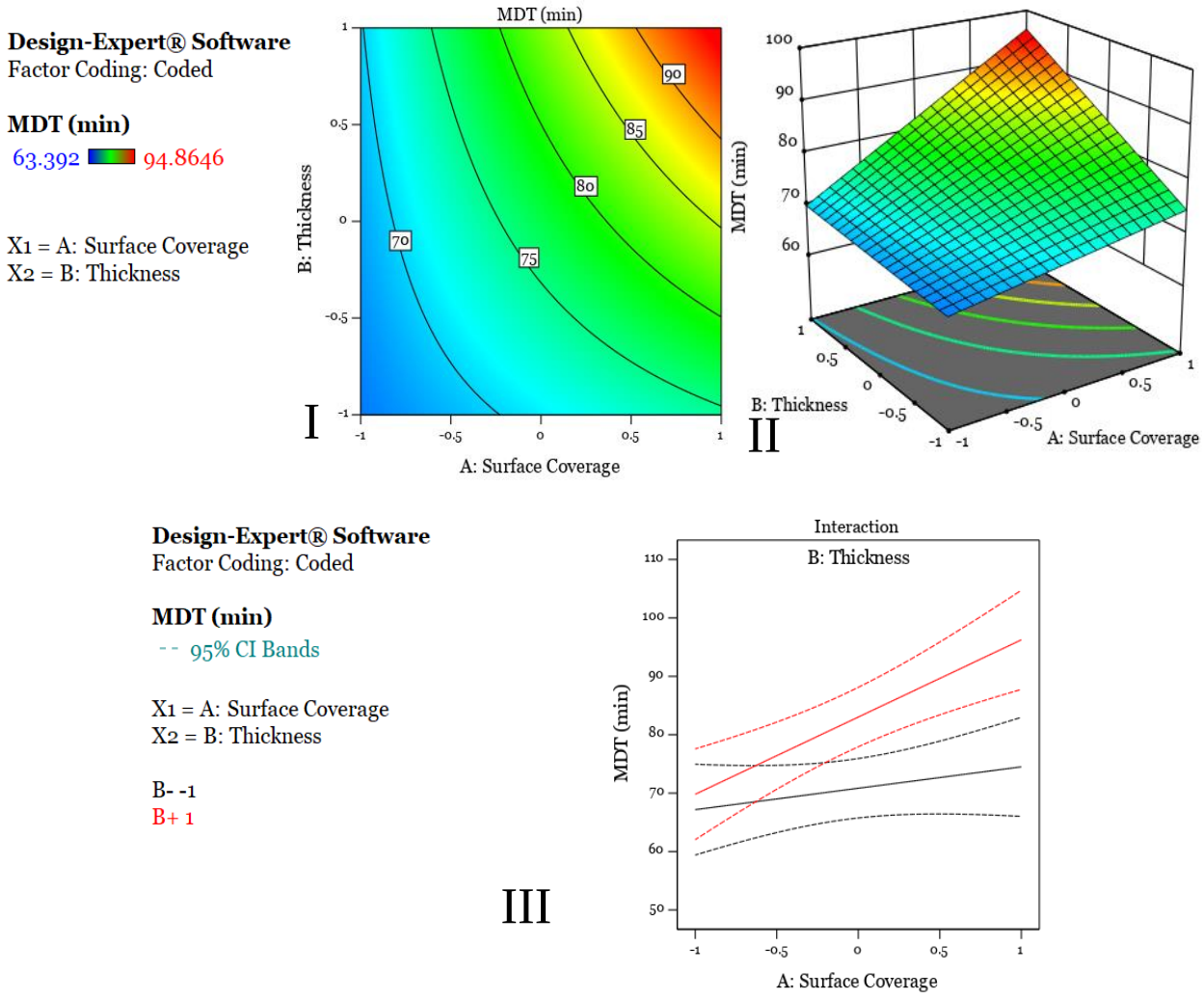


Figure III.6: Plots for Melevodopa One-sided coated tablets. Both factors are expressed in a coded scale from −1 to +1, with −1 being the lowest level and +1 being the highest. (I) Contour plot, Surface Coverage vs Thickness. (II) 3D Surface plot, Surface Coverage and Thickness vs MDT. (III) Interaction Plot, Surface Coverage and Thickness vs MDT.

The dissolution profiles (Figure III.7) also depict that the increase of both factors result in retardation of the API release, as well as that as the surface coverage becomes denser, the effect of the number of layers is more pronounced.

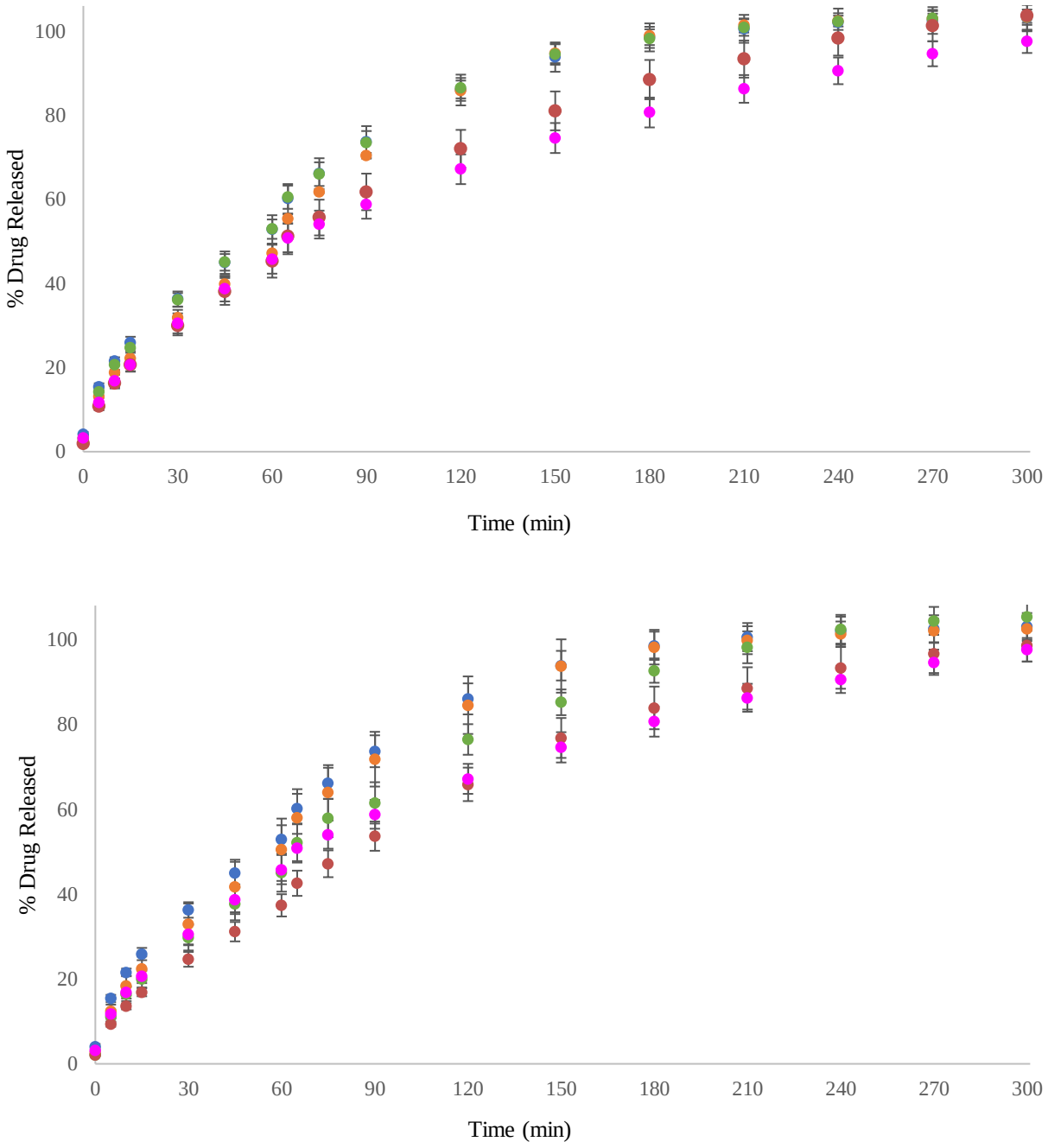


Figure III.7: Dissolution profiles of uncoated and one side coated Melevodopa tablets; mean value ± SD (n = 3). (Top) Factor A varies from 25% to 100% while factor B is constant at 8 layers. Blue circle: uncoated tablets, orange circle: factor A = 25%, green circle: factor A = 50%, red circle: factor A = 75% and pink circle: factor A = 100%. (Bottom) Factor A is constant at 100% while factor B varies from 2 to 8 layers. Blue circle: uncoated tablets, orange circle: factor B 2 layers, green circle: factor B 4 layers red circle: factor B 6 layers and pink circle: factor B 8 layers.

Design II: Melevodopa two-sides coated tablets

The second design performed for the hydrophilic API corresponds to the two-sided coated tablets. The combinations of factors A and B along with the selected response are presented in Table III.4.

Table III.4: Experimental design for Melevodopa tablets coated on two sides.

Run	Factor A: Surface Coverage (%)	Factor B: Thickness (No. Layers)	Response: MDT (min)
1	50	6	79.85 ± 1.14
2	100	4	100.62 ± 5.06
3	50	4	74.53 ± 1.18
4	100	2	89.31 ± 2.78
5	25	2	65.02 ± 4.28
6	75	2	84.98 ± 5.43
7	75	6	100.08 ± 1.19
8	25	4	69.30 ± 3.11
9	100	6	111.22 ± 1.12
10	50	8	85.54 ± 2.46
11	50	2	2 66.57 ± 1.96
12	100	8	111.38 ± 4.48
13	25	6	69.84 ± 2.07
14	25	8	71.22 ± 2.11
15	75	8	107.76 ± 0.77
16	75	4	91.07 ± 1.12

For the two-sided coated Melevodopa tablets the same pattern was identified as with the one-side coated tablets. Figure III.8 illustrates the results in detail. However, coating of tablets on both sides resulted in more extended MDT values when compared with the ones of the one-sided tablets. The ANOVA analysis showed that factors A, B and AB were significant ($p < 0.05$). The increase of factors A and B resulted in an increased MDT. For the interaction AB, the effect of factor B on MDT is more pronounced when factor A is at its highest level. Meaning that when the surface coverage is higher, the effect of the number of layers on MDT is more pronounced. In other words, as the coating becomes thicker and denser, MDT is affected in a greater extend compared to a thinner coating even if the surface coverage increases in the same manner. The equation describing this relationship is as followed:

$$MDT = +86.14 + 18.33 \cdot A + 8.83 \cdot B + 4.23 \cdot AB \qquad \textit{Eq. III.2}$$

where MDT is expressed in min, A: Surface Coverage, B: Thickness and $-1 < A, B < 1$.

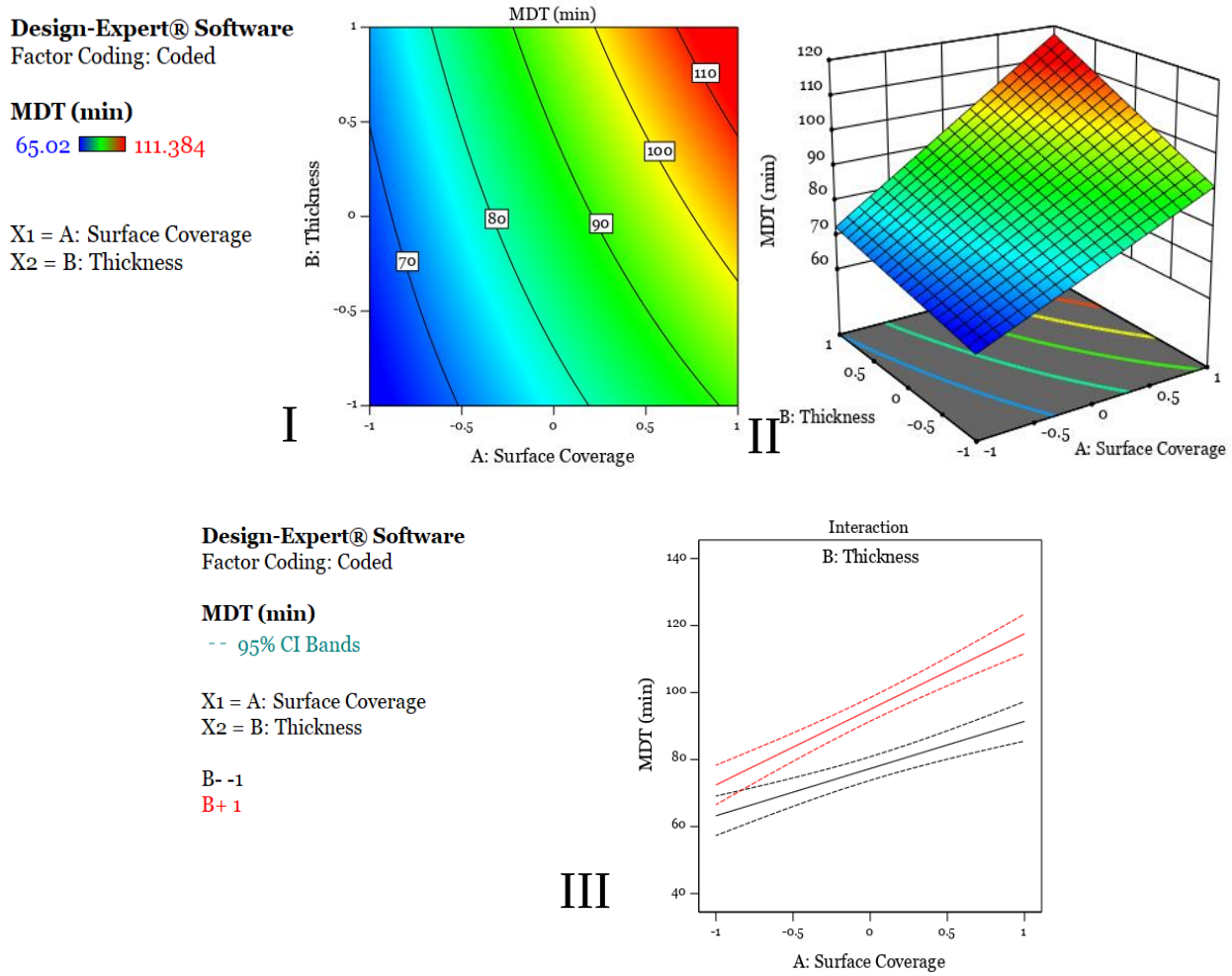


Figure III.8: Plots for Melevodopa two-sided coated tablets. Both factors are expressed in a coded scale from −1 to +1, with −1 being the lowest level and +1 being the highest. (I) Contour plot, Surface Coverage vs Thickness. (II) 3D Surface plot, Surface Coverage and Thickness vs MDT. (III) Interaction Plot, Surface Coverage and Thickness vs MDT.

The following Figures (Figure III.9 and Figure III.10) depict the release profile of Melevodopa two-sides coated tablets for various levels of factor A and B as well as the comparison of Melevodopa one-side versus two-sides coated tablets. For the two-sides coated tablets, the increase of factors A and B resulted in a higher retardation of the API release and most importantly, when the surface coverage is denser, the effect of the number of layers on the release rate is more pronounced. Furthermore, as shown in Figure III.10, coating on both sides of the tablet results in a slower release compared to the one-side coating. As both factors A and B increase, this effect is more pronounced. For example, after 1 h, the release of the API from the uncoated tablet is 53% and after 2 h is 86%. When factor A is 75% and factor B is 6 layers, the one-side coated tablet shows 47% release which becomes 72% after 2 h. On the other hand, the two-sides coated tablet shows 37% release and 61% respectively. As factors A and B increase (A = 100% and B = 8 layers), the corresponding release decreases to 45% and 67% for the one-side coated tablet and 31% to 51% for the two-sides coated tablet.

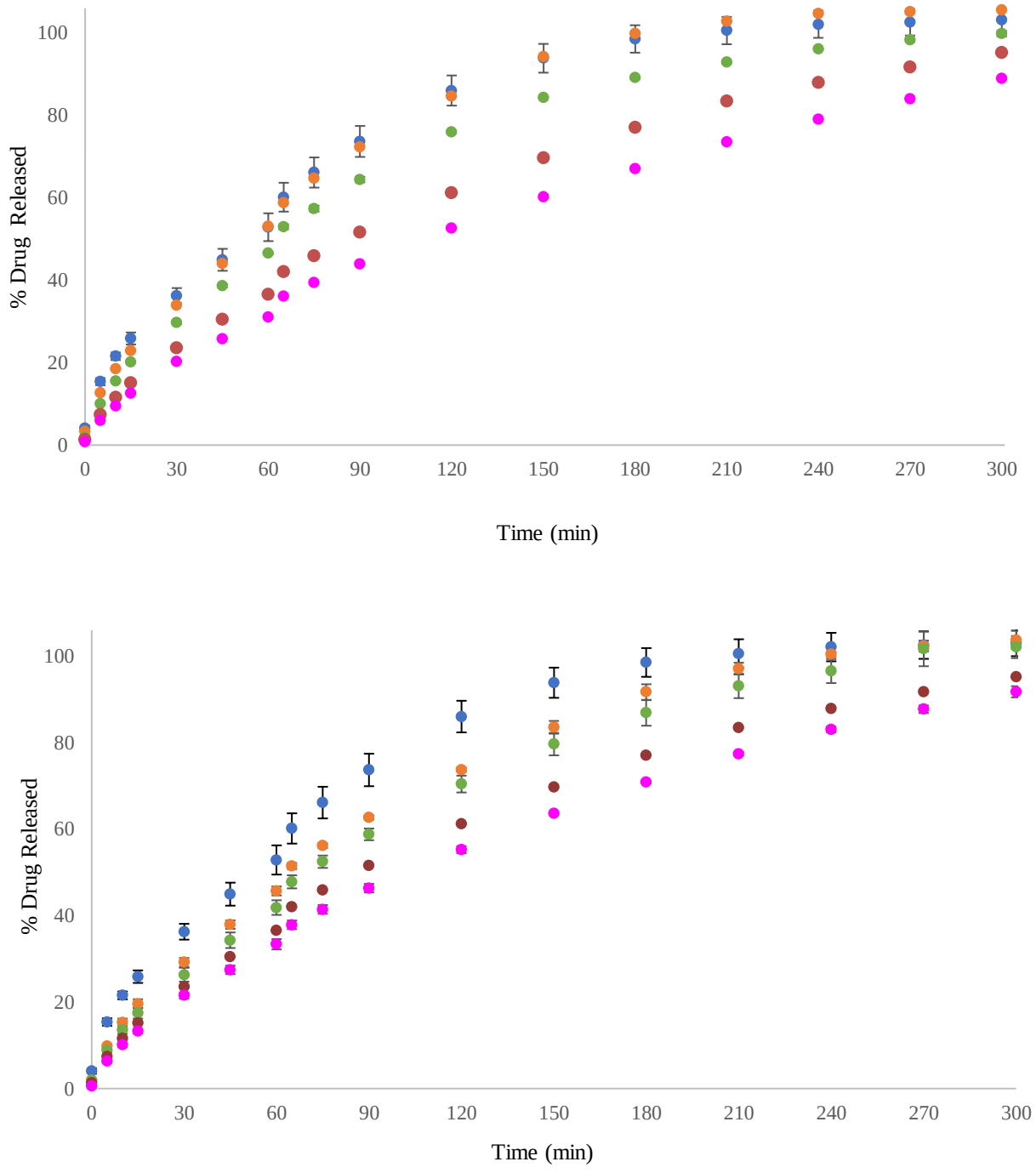


Figure III.9: Dissolution profiles of uncoated and two-sides coated Melevodopa tablets; mean value ± SD (n=3). (Top) Factor A varies from 25% to 100% while factor B is constant at 6 layers. Blue circle: uncoated tablets, orange circle: factor A=25%, green circle: factor A=50%, red circle: factor A=75% and pink circle: factor A=100%. (Bottom) Factor A is constant at 75% while factor B increases from 2 to 8 layers. Blue circle: uncoated tablets, orange circle: factor B 2 layers, green circle: factor B 4 layers, red circle: factor B 6 layers and pink circle: factor B 8 layers

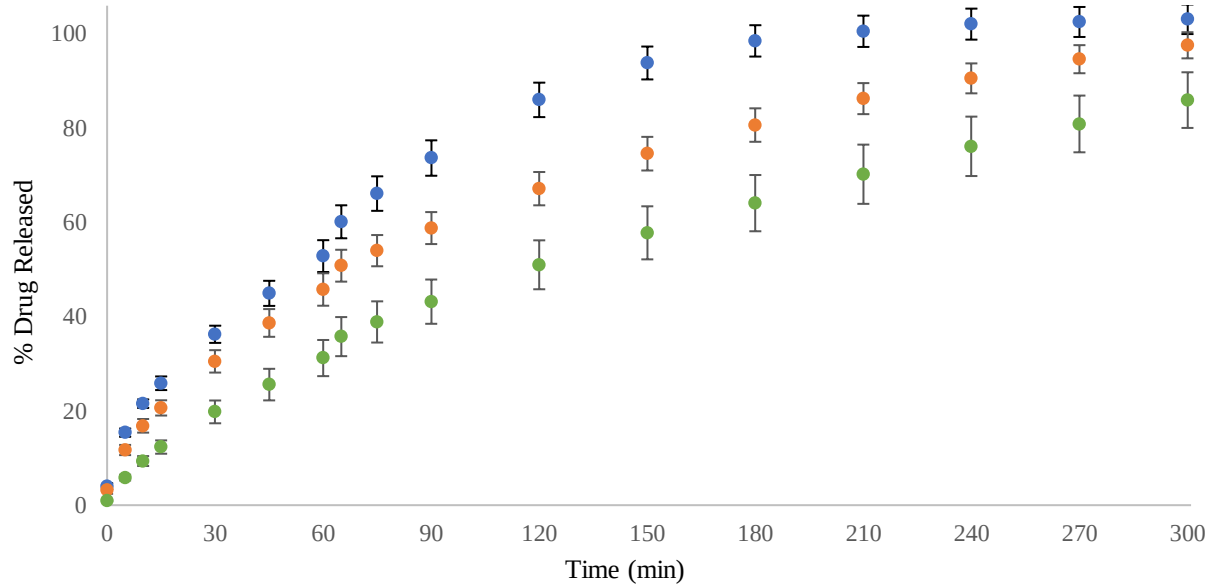


Figure III.10: Dissolution profiles of uncoated versus one-side and two-sides coated Melevodopa tablets; mean value ± SD (n=3). Factor A is constant at 100% and factor B at 8 layers. Blue circle: uncoated tablets, orange circle: one-side coated tablet and green circle: two-sides coated tablets.

Design III: Acyclovir one-side coated tablets

As for Melevodopa, the first design performed for the lipophilic API corresponds to the core tablets being coated on one side. The combinations of factor A and B at four levels are depicted in Table III.5.

Table III.5: Experimental design for Acyclovir tablets coated on one side.

Run	Factor A: Surface Coverage (%)	Factor B: Thickness (No. Layers)	Response: MDT (min)
1	50	8	128.13 ± 2.31
2	50	6	121.49 ± 8.13
3	100	4	125.12 ± 9.45
4	75	6	115.35 ± 2.66
5	25	6	128.53 ± 5.20
6	100	6	120.12 ± 6.42
7	25	2	135.78 ± 8.95
8	50	2	128.73 ± 5.05
9	100	2	137.20 ± 4.25
10	50	4	113.12 ± 1.62
11	75	4	121.29 ± 6.15
12	25	8	129.27 ± 4.51
13	75	8	115.54 ± 9.61
14	25	4	113.87 ± 5.30
15	100	8	120.82 ± 6.51
16	75	2	134.25 ± 4.04

The analysis of results for the lipophilic API one-side coated tablets revealed some remarkable differences compared the hydrophilic API. The results are depicted in detail in Figure III.11. In this case, ANOVA analysis revealed the quadratic model as significant and the terms which affect the MDT were B, AB, and B^2 ($p<0.05$).

$$MDT = +116.19 - 0.6606 \cdot A - 4.30 \cdot B - 4.87 \cdot AB + 4.61 \cdot A^2 + 9.96 \cdot B^2 \quad \textit{Eq. III.3}$$

where, MDT is expressed in min, A: Surface Coverage, B: Thickness and -1<A, B<1.

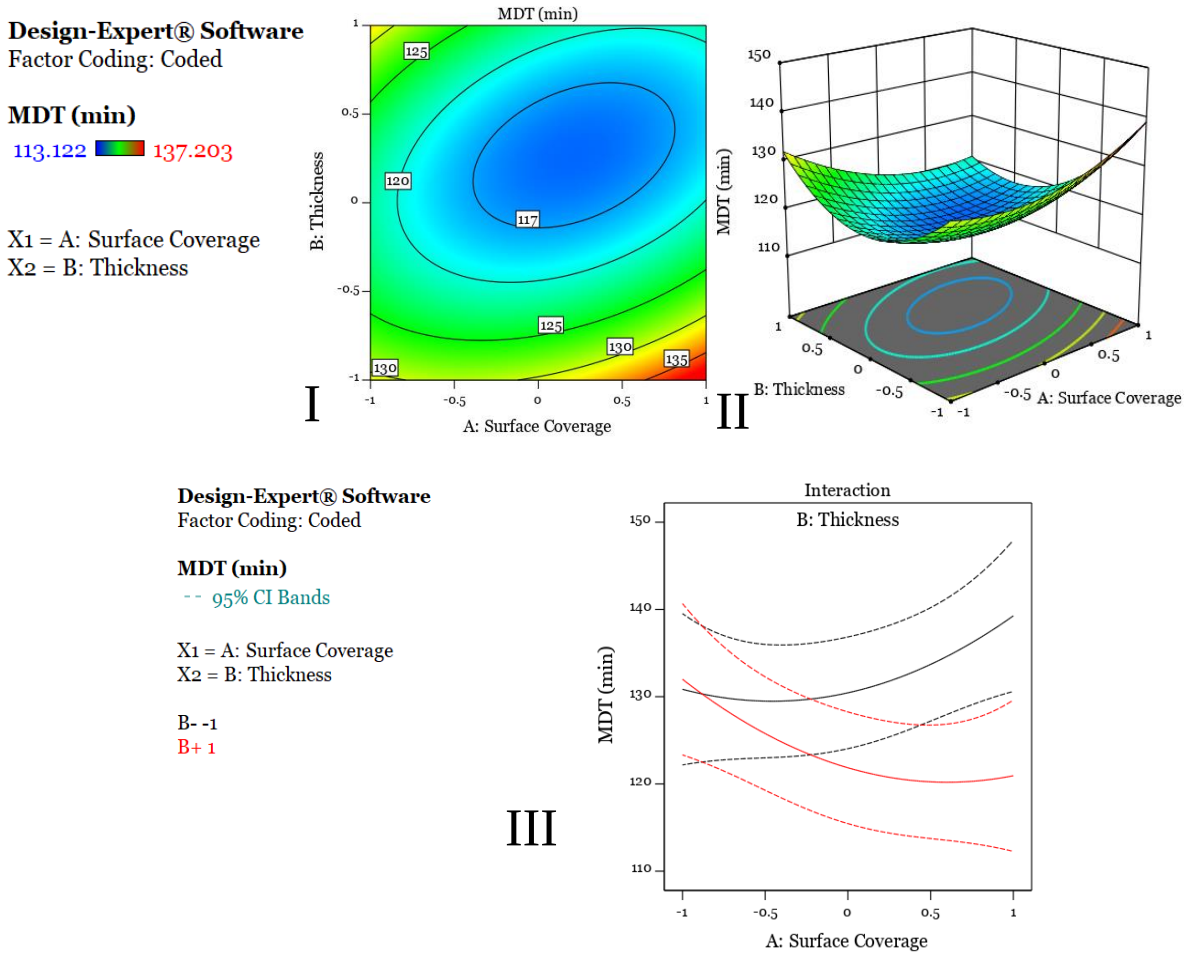


Figure III.11: Plots for Acyclovir One-side coated tablets. Both factors are expressed in a coded scale from -1 to +1, with -1 being the lowest level and +1 being the highest. I) Contour plot, Surface Coverage vs Thickness. II) 3D Surface plot, Surface Coverage and Thickness vs MDT. III) Interaction Plot, Surface Coverage and Thickness vs MDT.

For the lipophilic Acyclovir one-side coated tablets, the AB interaction revealed that the effect of factor B on MDT in more pronounced when factor A is at its highest level. This means that the effect of the number of layers on the selected response is more pronounced when the surface coverage is high. In other words, when the coating is thin and as it becomes denser, MDT is affected in a greater extent than a thicker coating even if the surface coverage increases in the same manner. This can be explained by considering that the lipophilic API first diffuses at the lipophilic coating and secondly to the dissolution medium, resulting in a higher retardation when the coating is either thick or dense.

The dissolution profiles (Figure III.12 and Figure III.13) of the lipophilic API depict that overall, the increase of both factors A and B result in retardation of the API release. However, when the coating is thin (e.g., 2 layers coating) regardless the surface coverage, the API release is higher than the uncoated tablet. This indicates probably that a thin lipophilic coating on the one side enhances the dissolution of the lipophilic API. This could explain the quadratic model characterizing the release from the one-side coated tablet.

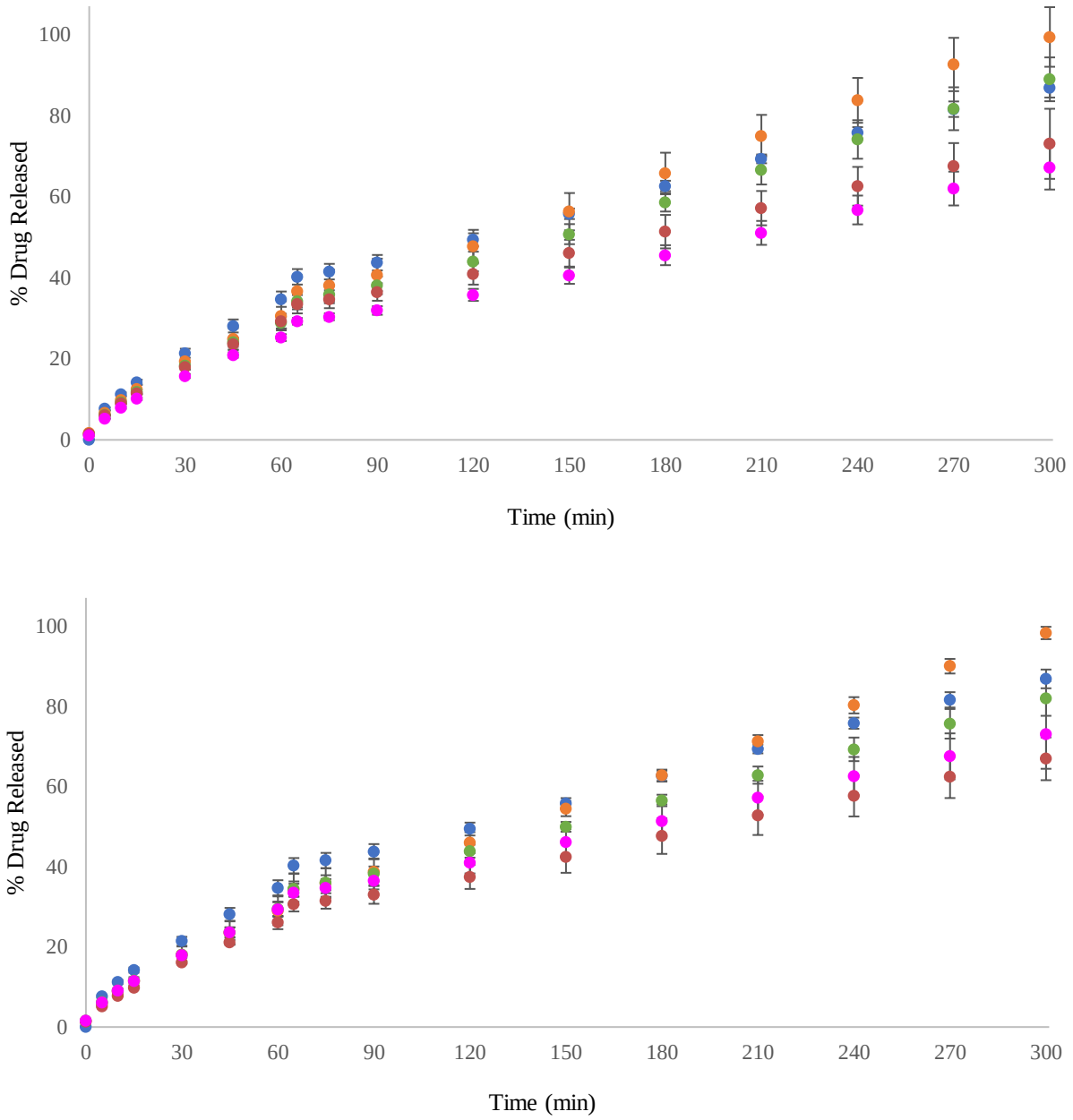


Figure III.12: Dissolution profiles of uncoated and one-side coated Acyclovir tablets; mean value ± SD (n=3). (Top) Factor A varies from 25% to 100% while factor B is constant at 8 layers. Blue circle: uncoated tablets, orange circle: factor A=25%, green circle: factor A=50%, red circle: factor A=75% and pink circle: factor A=100%. (Bottom) Factor A is constant at 75%, while factor B varies from 2 to 8 layers. Blue circle: uncoated tablets, orange circle: factor B 2 layers, green circle: factor B 4 layers, red circle: factor B 6 layers and pink circle: factor B 8 layers.

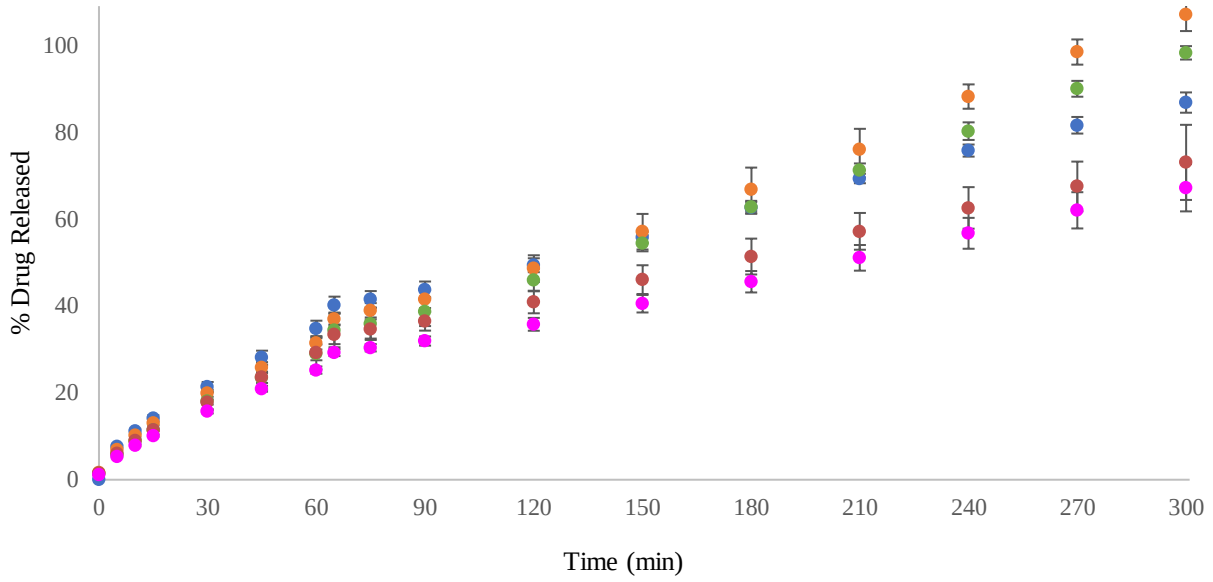


Figure III.13: Dissolution profiles of uncoated and one-side coated Acyclovir tablets; mean value ± SD (n=3). Blue circle: uncoated tablets, orange circle: factor A=25% and B 2 layers, green circle: factor A=75% and B 2 layers, red circle: factor A=75% and B 8 layers and pink circle: A=100% and factor B 8 layers.

Design IV: Acyclovir two-sides coated tablets

The second design performed for Acyclovir corresponds to the tablets coated on both sides. The combinations of factors A and B along with the selected response are presented in Table III.6.

Table III.6: Experimental design for Acyclovir tablets coated on two sides.

Run	Factor A: Surface Coverage (%)	Factor B: Thickness (N. Layers)	Response: MDT (min)
1	75	6	131.67 ± 4.37
2	50	6	115.44 ± 8.45
3	100	2	125.61 ± 9.87
4	50	4	116.41 ± 6.54
5	50	2	106.21 ± 5.14
6	25	8	121.10 ± 4.51
7	100	6	139.37 ± 3.96
8	100	4	125.09 ± 2.53
9	25	4	110.90 ± 10.08
10	75	2	118.76 ± 8.23
11	25	6	111.68 ± 3.34
12	75	4	126.92 ± 6.93
13	75	8	128.05 ± 2.51
14	25	2	111.06 ± 4.00
15	100	8	128.96 ± 3.72
16	50	8	124.06 ± 4.14

The two-sides coated Acyclovir tablets showed a similar but not identical behavior with the hydrophilic API as factors A and B were found significant but not their interaction. The results are depicted in detail inFigure III.14: Plots for Acyclovir Two-side coated tablets. Both factors are expressed in a coded scale from -1 to +1, with -1 being the lowest level and +1 being the highest. I) Contour plot, Surface Coverage vs Thickness. II) 3D Surface plot, Surface Coverage and Thickness vs MDT. III) Interaction Plot, Surface Coverage and Thickness vs MDT.Figure III.14. Like the hydrophilic API, the increase in factors A and B result in an increased MDT, meaning that as the surface of the tablet is covered with a thicker coating, the release of the API is lower. The model describing the relation of the MDT as a function of factors A and B is presented in the following equation:

$$MDT = +121.33 + 8.86 \cdot A + 5.27 \cdot B \qquad \textit{Eq. III.4}$$

where, MDT is expressed in min, A: Surface Coverage, B: Thickness and -1<A, B<1.

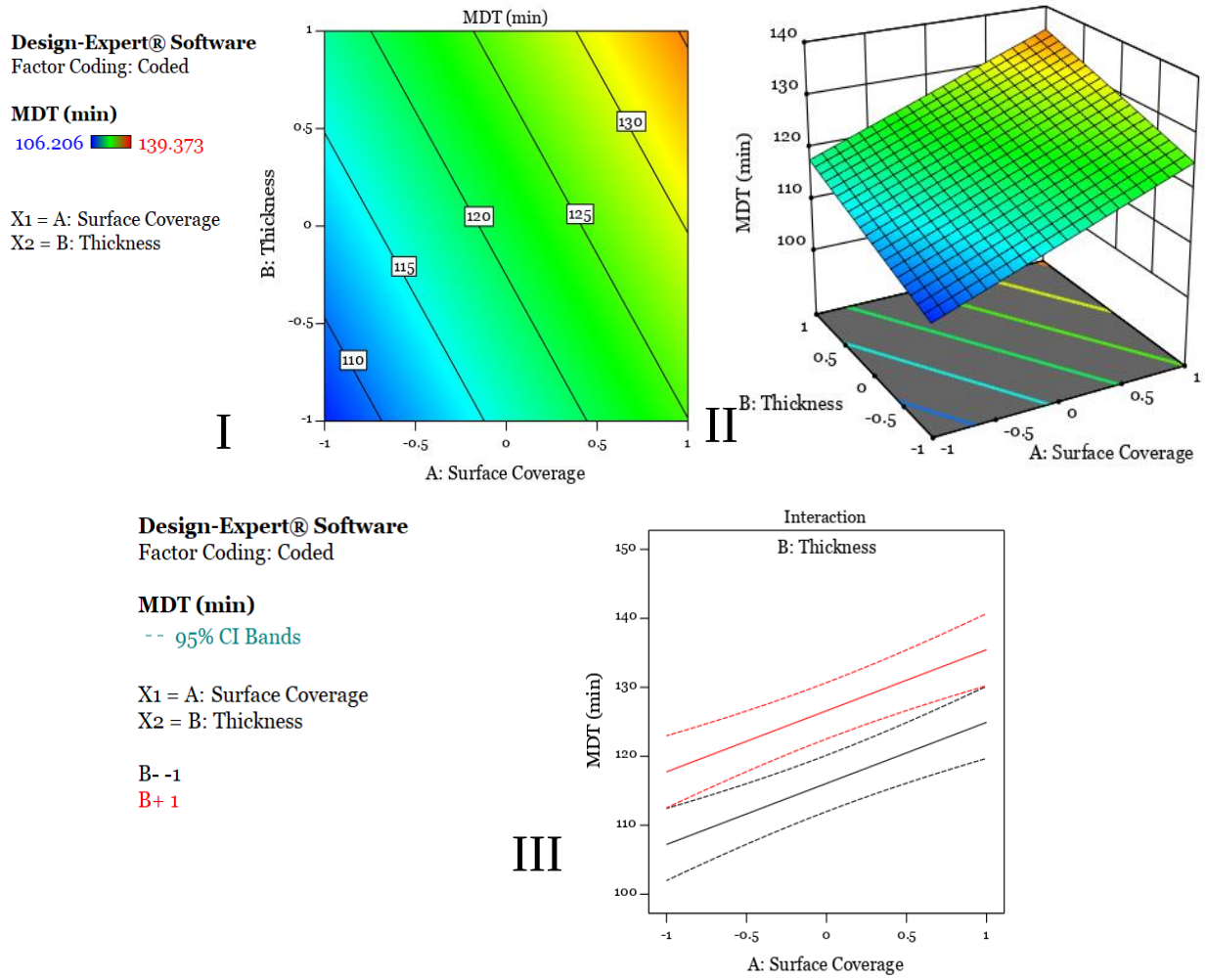


Figure III.14: Plots for Acyclovir Two-side coated tablets. Both factors are expressed in a coded scale from -1 to +1, with -1 being the lowest level and +1 being the highest. I) Contour plot, Surface Coverage vs Thickness. II) 3D Surface plot, Surface Coverage and Thickness vs MDT. III) Interaction Plot, Surface Coverage and Thickness vs MDT.

Figure III.15 depicts the release profile of Acyclovir two-sides coated tablets for various levels of factor A and B, while Figure III.16 illustrates the comparison of Acyclovir uncoated, one-side and two-sides coated tablets. For the two-sides coated tablets, as shown in the first two figures, the increase of both factors A and B resulted in a higher retardation of the API release compared to the uncoated tablets. For example, after 120 min, for the uncoated tablets, the release of the API is at 50%, while for the 50% 4-layer coating the respective release is 8% less, for the 50% 8-layer coating is 15% less and for the 100% 8-layer coating the API release is half from the uncoated. Thus, as the coating becomes denser and thicker, the release of the API is lower. Regarding the comparison between the one-side and two-sides coating, as shown in Fig. 20, it can be concluded that as both factors A and B increase, coating on both sides of the tablet results in a slower API release profile.

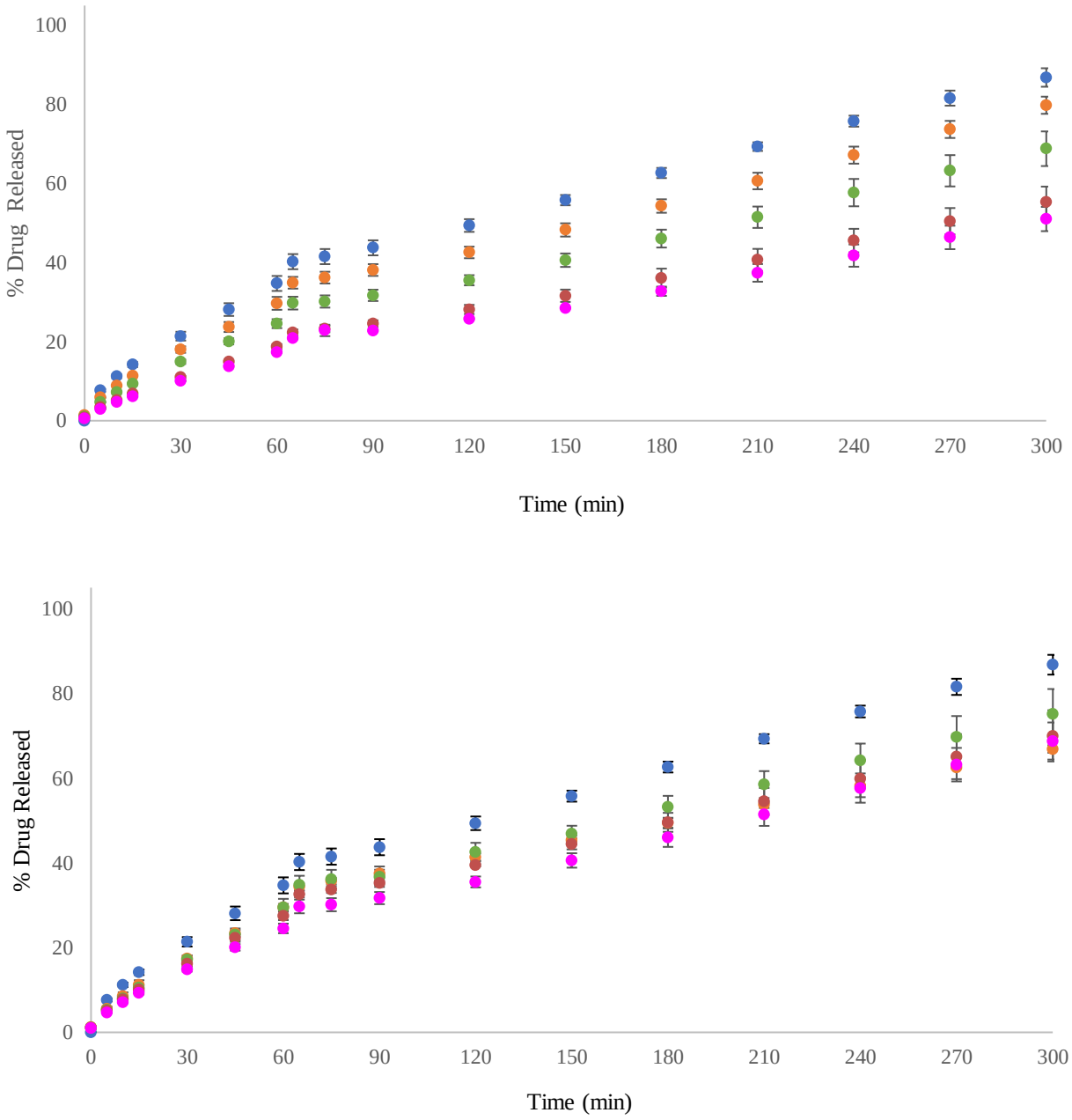


Figure III.15: Dissolution profiles of uncoated and two-sides coated Acyclovir tablets; mean value ± SD (n=3). (Top) Factor A varies from 25% to 100% while factor B is constant at 8 layers. Blue circle: uncoated tablets, orange circle: factor A=25%, green circle: factor A=50%, red circle: factor A=75% and pink circle: factor A=100%. (Bottom) Factor A is constant at 50%, while factor B varies from 2 to 8 layers. Blue circle: uncoated tablets, orange circle: factor B 2 layers, green circle: factor B 4 layers, red circle: factor B 6 layers, and pink circle: factor B 8 layers.

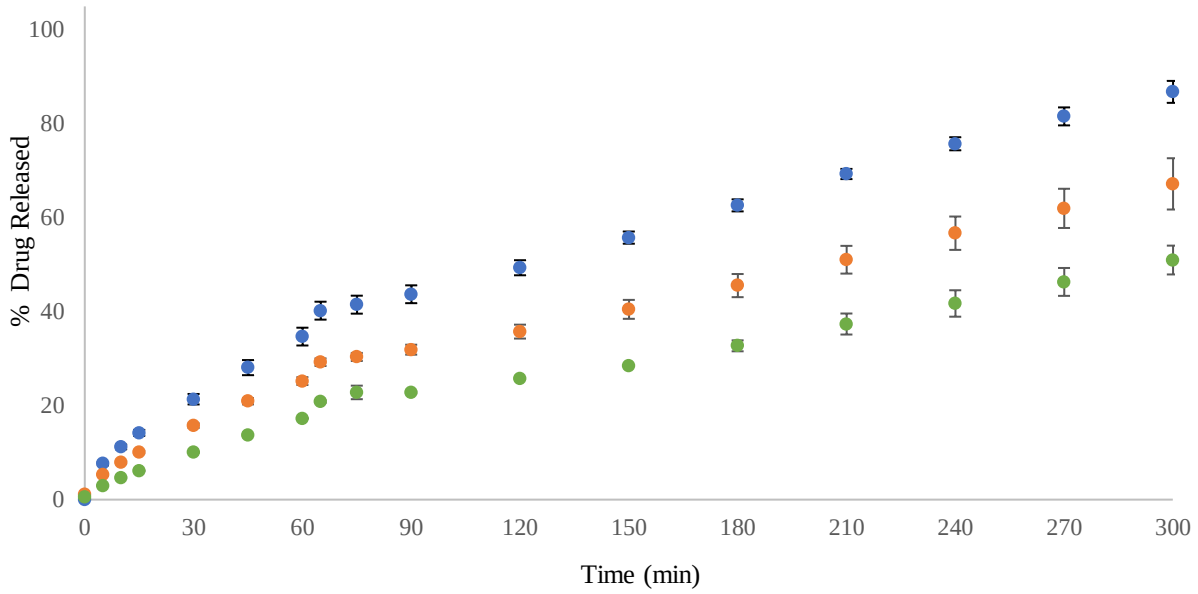


Figure III.16: Dissolution profiles of uncoated versus one-side and two-sides coated Acyclovir tablets; mean value ± SD (n=3). Factor A is constant at 100% and factor B at 8 layers. Blue circle: uncoated tablets, orange circle: one-side coated tablet and green circle: two-sides coated tablets.

Overall Experimental Design Results

The significant terms and interactions which affect the MDT of both APIs are depicted in Table III.7. It can be concluded that factors A, B and their interaction AB proved significant in most of the cases. For the one side coated Acyclovir tablets the model describing the relation of the MDT as a function of the selected factors was quadratic and factor A did not prove to be significant, while for the two-sided coated tablets the model was linear, and the significant terms were only factors A and B. For the one-side coated Melevodopa tablets, the interaction AB was marginally not significant. In all cases however, factor B was found significant regardless of the API and the number of coated sides.

Table III.7: Terms with significant effect on the MDT. A: Surface Coverage , B: Thickness, S: Significant, NS: Non-Significant.

Tablet	**Terms**				
	A	B	AB	A^2	B^2
Melevodopa (One-side coating)	S	S	NS	-	-
Melevodopa (Two-sides coating)	S	S	S	-	-
Acyclovir (One-side coating)	NS	S	S	NS	S
Acyclovir (Two-sides coating)	S	S	-	-	-

As depicted in the above results, the release of both APIs is altered according to the number of layers of coating material applied, the percentage of the surface covered as well as the number of tablet sides coated.

This attribute is particularly useful as differences in patients (e.g. age, race or weight) can lead to variability in the therapeutic effect of the selected dosage form. A tool such as the one proposed that combines 3DP and statistical correlations would allow easy, flexible, and rapid modification of the release of the API according to the patient's needs and can offer the desired therapeutic effect, at the point of need and at the time of need. Especially in cases where the therapeutic index is narrow, this approach can help for the optimal outcome.

III.1.3. Kinetic Model and Release Mechanism

In both APIs, regardless of the levels of the coating parameters, the release kinetics were found to be non-Fickian. For the uncoated Melevodopa tablets the exponent n determined according to $\frac{M_t}{M_0} = k \cdot t^n$ Eq. II.3 was 0.51 ± 0.04, while for the uncoated Acyclovir tablets was 0.61 ± 0.004. The one and two-sided coated Melevodopa tablets exhibited an exponent n which varied between 0.52 and 0.60 and 0.59–0.73 respectively. For the lipophilic API, all exponent values were found between 0.61 and 0.70, for the one-side and between 0.62 and 0.74 for two-sided coated tablets. In conclusion, regardless of the type of API, number of coated sides and the levels of the surface coverage layers applied, n exponents fall within the non-Fickian transport range, which showed that the dissolution profiles can be controlled without affecting the kinetic mechanism.

The uncoated tablets of both APIs can be regarded as swellable matrix tablets, at which the interaction between the dissolution medium, the hydrophilic polymer and the drug are the primary factors which control the release. In other words, the release mechanism is driven by a gel layer forming around the matrix due to water penetration, polymer swelling, drug dissolution and diffusion as well as matrix erosion. The drug diffusion through the gel layer and/or erosion of the gel layer control the drug release (Colombo et al., 1996).

In the same manner, for the coated tablets, the release of the API is controlled by the diffusion through the gel layer and/or erosion of the gel layer at the free surfaces. However, in this case, an extra barrier is applied, the lipophilic-insoluble coating, which allows water penetration mainly through the free, in-between spaces and the lateral surface. Thus, erosion of the gel layer and diffusion through the coating are limited. When the tablets are coated on one-side, the release is mainly governed through the free side, while for the two-sides coated tablets, the release is hindered due to the less available free surface. These findings were in agreement with Pereira et al. (Pereira et al., 2019), who constructed 4-layer 3D printed tablets with each layer containing different API, at which the release profile depended on the position of the layer. The drugs in the inner layers dissolved only after diffusion of liquid inwards from the top and lower layers and by erosion from the outermost part of the layer. As, the top and bottom layers dissolved, the diffusion from the middle layers to the dissolution medium was more accessible. In the same way, when the tablets are coated with the glyceride, the diffusion from the inner region becomes more accessible as surface coverage, coating thickness and coated sides decrease.

III.2. A 3D Printing and Machine Vision Application for Quality Risk Management in Compounding Drug Products at the Point of Need

III.2.1. System's Design

Community and Hospital Pharmacies prepare compounded drug products on site, following a prescription issued to address a special patient need not met by marketed alternatives. According to the recent relevant guidance, Pharmacy preparations should comply with specific quality criteria to assure their safety and efficacy profile. This new framework practically promotes the implementation of cGood Manufacturing Practices (cGMPs), Quality by Design (QbD) and Quality Risk Management (QRM) as enablers for meeting these new requirements. Within this context, the scope of this work is to present an approach for automated quality control of compounded drug products prepared at the point of need with the use of a 3D printing (3DP) process, taking into consideration the fundamental quality guidelines applied for finished pharmaceuticals.

3DP could be a realistic tool for addressing on-demand manufacturing of drug products fitting the special needs of a patient, such as the case of compounding. Its flexibility, precision, speed, robustness, and cost-effectiveness have rendered 3DP an innovative and promising technology, which could be a basic preparation station of small batches. When coupled with the additional technological parts of the proposed design and supported by a cloud-based system, this portable multipurpose equipment could successfully address the new quality requirements of the products prepared in Community or Hospital Pharmacies by rationally mitigating the risks associated with the compounding practices.

A schematic representation and a flow diagram of a system that is able to prepare orodispersible films by 3DP and at the same time perform all the relevant quality controls is depicted in Figure III.17 and Figure III.18.

The compounding process begins with the API selection and formulation development. It is assumed that the formulation and process development of the final bulk solution conducted within the QbD framework, has been successfully carried out by an approved supplier. The sealed container with the product, which is properly released through the standard Quality Assurance procedures by the provider, is received by the Pharmacy and represents the ready to use formulation. This product is tested on site for assuring its identity and %Assay with an appropriate analytical method such as FT-IR, Raman, or UV/Vis. These processes can be performed either on-line or at-line, separately from the rest of the process followed. Subsequently and if conformed to the specs, the checked formulation can be loaded to the 3D printer in order to prepare the personalized orodispersible films. The operator can control a series of the proposed system inputs such as the number of films to be printed, the size of the film, the printing speed, layer count or path width. The process monitoring and control equipment is in place in order to perform the in-process controls. The steps required for carrying out the whole production process and the relevant QC tests are presented in detailed at the Master Manufacturing Formula, records which describe the production stages and any relevant process parameters and thus can be easily followed by the trained Pharmacist and recorded. After the production of the 3D printed films, they are checked in terms of dose accuracy through weighing, API identification and for defects through Machine Vision. If one of the above is not conforming with the quality aspects defined in the system, then the out of specifications films are discarded. The conforming films that pass the above-mentioned checks are left to dry. In the same manner, the dry films are checked for dose accuracy, API identification and assay as well as for defects. Again, if one of the above quality

characteristics is not conforming, the prepared films are discarded. The conforming films that pass the final quality checks are able to be released and administered.

A cloud-based system effectively manages the above together with a series of supporting activities such as scheduling, maintenance, reporting/filing, SOPs etc., which can all be filed and remotely accessed, while maintaining data integrity. Therefore, the entire supply chain of a personalized drug product, from its raw materials and through its manufacturing process to the patient, is quality assured, recorded and fully traceable through a reliable systems thinking and acting approach.

The above design adequately addresses the risks associated with receiving the wrong API, contamination issues and dose accuracy through an automated Quality Control subsystem that simultaneously performs identification, weight, assay, and integrity checking in real time, while at the same time the whole production process can be monitored remotely.

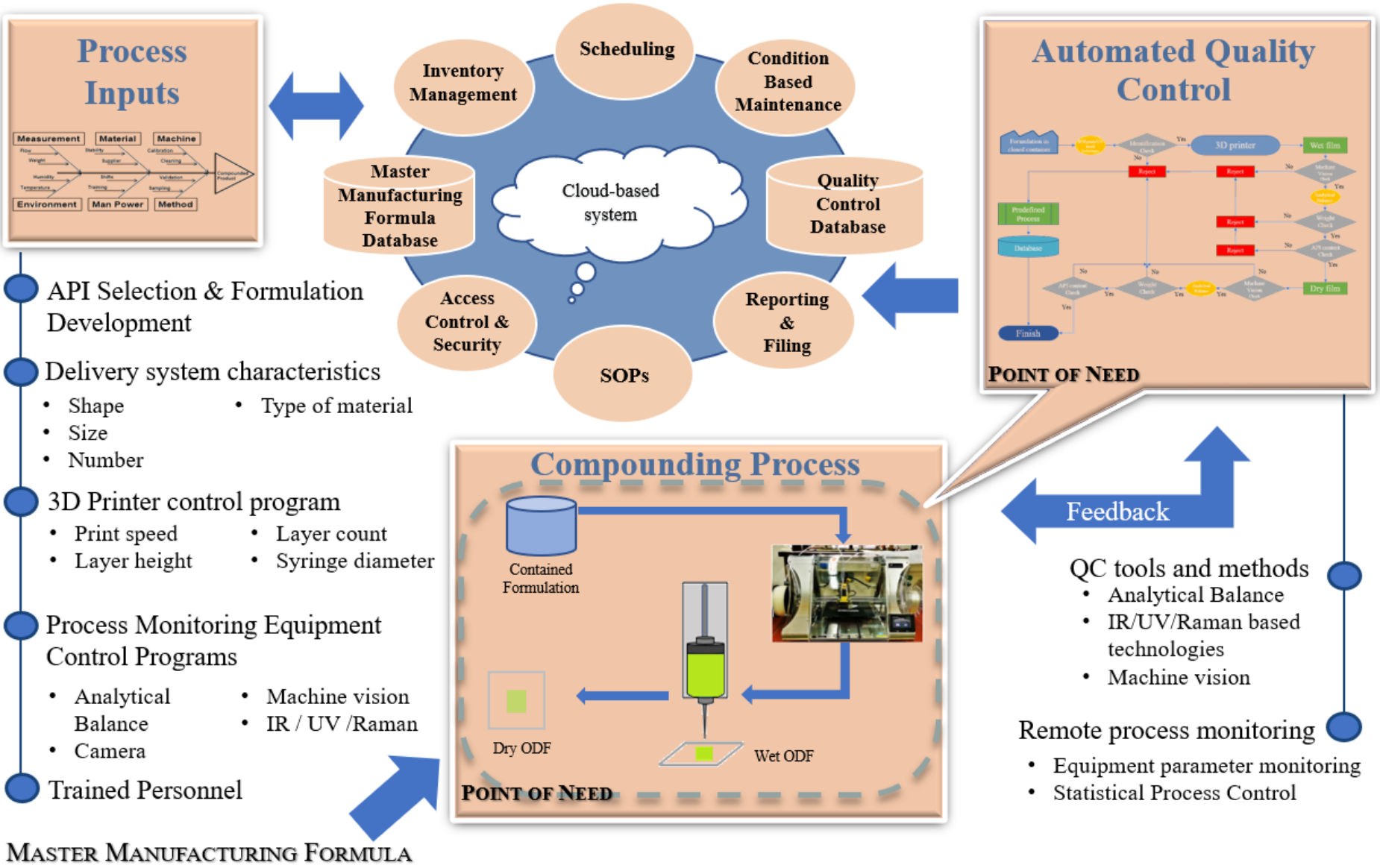


Figure III.17: Pharma 4.0 system for risk mitigation of compounded drug products at the point of need.

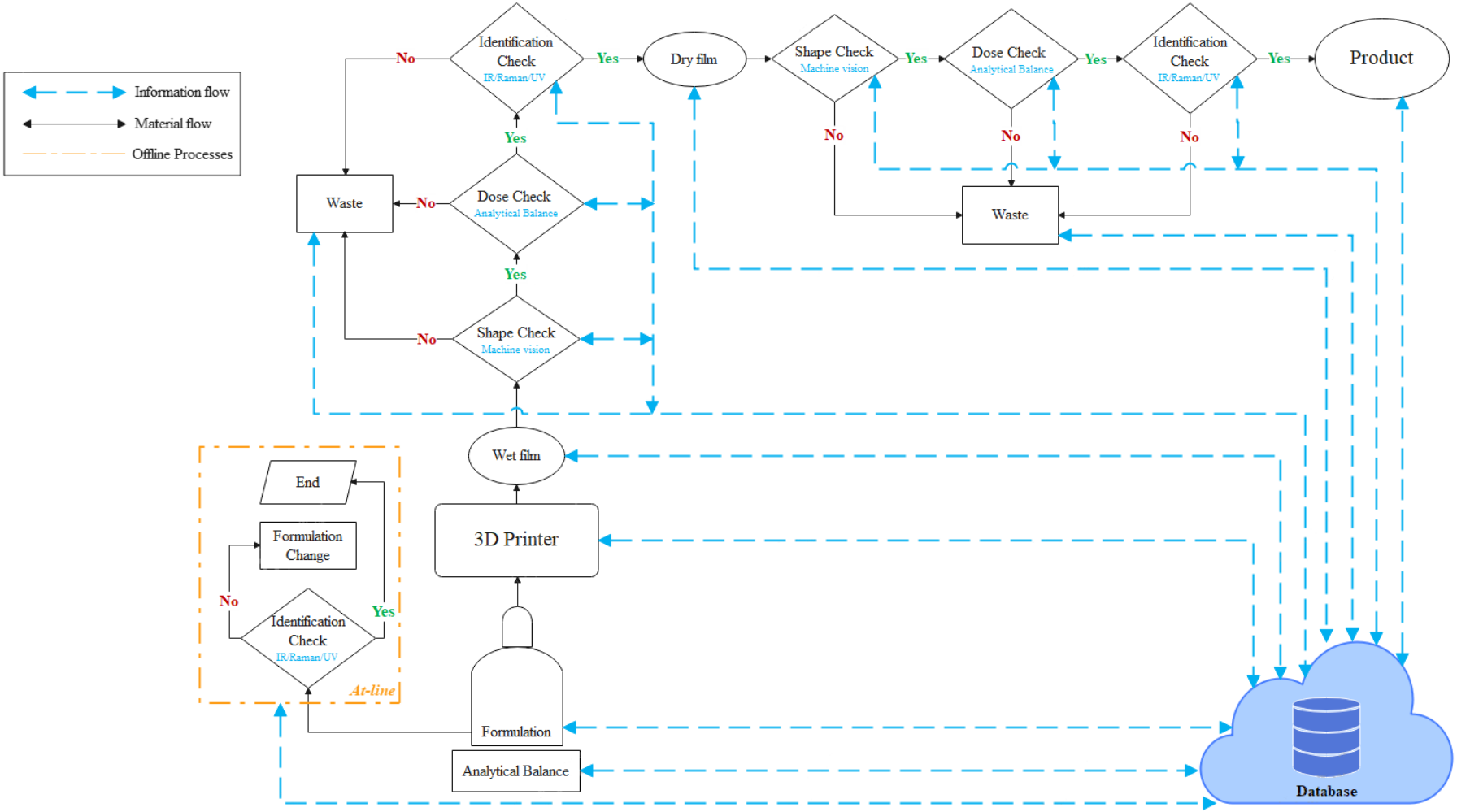


Figure III.18: Flow Diagram of the compounding process steps, and the relevant quality controls tools coupled with the information storage and traceability.

III.2.2 In-process controls

Raw Materials Control

The bulk gel used for the orodispersible films production consisted of the API, Warfarin Sodium, Hypromellose, and purified water. All raw materials were subjected to identification check via UV, IR, and Raman spectroscopy. Initially, Warfarin Sodium was dissolved in purified water to various concentrations and scanned through the whole spectrum (190-800 nm) (Figure III.19) in order to identify the λ_{max}, which proved to be in accordance with the bibliographic data at 308 nm (European Directorate for the Quality of Medicines & Healthcare (EDQM) & Council of Europe, 2019), as well as define the minimum and maximum concentrations at which the absorbance is between 0.1-1. Hypromellose and water did not show any absorbance at 308 nm.

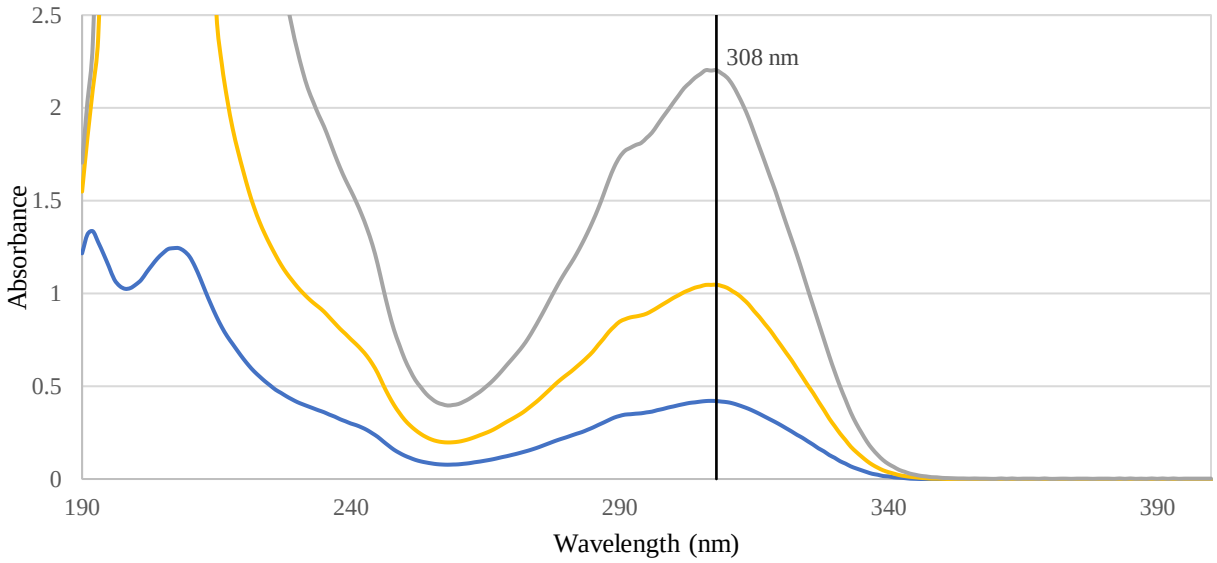


Figure III.19: UV absorbance of Warfarin sodium at different concentrations. Blue line: 0.01 mg/ml, yellow line: 0.025 mg/ml and grey line: 0.05 mg/ml

In the same manner, all raw materials were subjected to FT-IR spectroscopy in order to identify the characteristic bands of each material, both with absorbance and transmittance mode (Figure III.20). In the FT-IR spectrum of water, two bands appear: a broad strong band at the wavelength range 3370-3250 cm^{-1} corresponding to the O-H stretching and a sharp medium band at 1630 cm^{-1}, which is the O-H bending. In the FT-IR spectrum of Hypromellose, two small broad bands appear at around 3500 cm^{-1} and 2900 cm^{-1} assigned to the stretching of the hydroxyl group and the C-H of the pyranoid ring respectively. The strong band at 1049 cm^{-1} corresponds to the C-O-C stretching vibration of the glycosidic bond of the cellulose, while the vibration of the -OCH_3 group gives a sharp medium band at 943 cm^{-1} (Lin-Vien et al., 1991; Velazquez et al., 2003).

At the region 4000 - 1750 cm^{-1} of the FT-IR spectrum of Warfarin sodium, no significant bands appear, whereas a wide set of peaks are present at 1730 - 650 cm^{-1}. The bands at 1700 - 1500 cm^{-1} are attributed to the stretching vibration of C=O and C=C while the bands within the range 1500 - 1300 cm^{-1} are attributed to the C-C and C-H stretching of the methylene and methyl groups. At 1260 - 1100 cm^{-1} some weak bands appear due to the in-plane C–H bend and at 900-650 cm^{-1} the out-of-plane C-H bending bands of the

aromatic ring appear. The most distinct band which was not overlapping with the other materials was at 1507 cm^{-1}. It is worth mentioning that the double bond absorptions are unique to warfarin in the formulation, thus analyzing a sample containing only these three components will theoretically be quite easy because the characteristic bands of warfarin are many and strong. Unless the warfarin sodium concentration is too low, that the water absorptions/transmittance will cover all peaks, even a very small amount of the active ingredient will appear, even if it only makes one "shoulder" in the range.

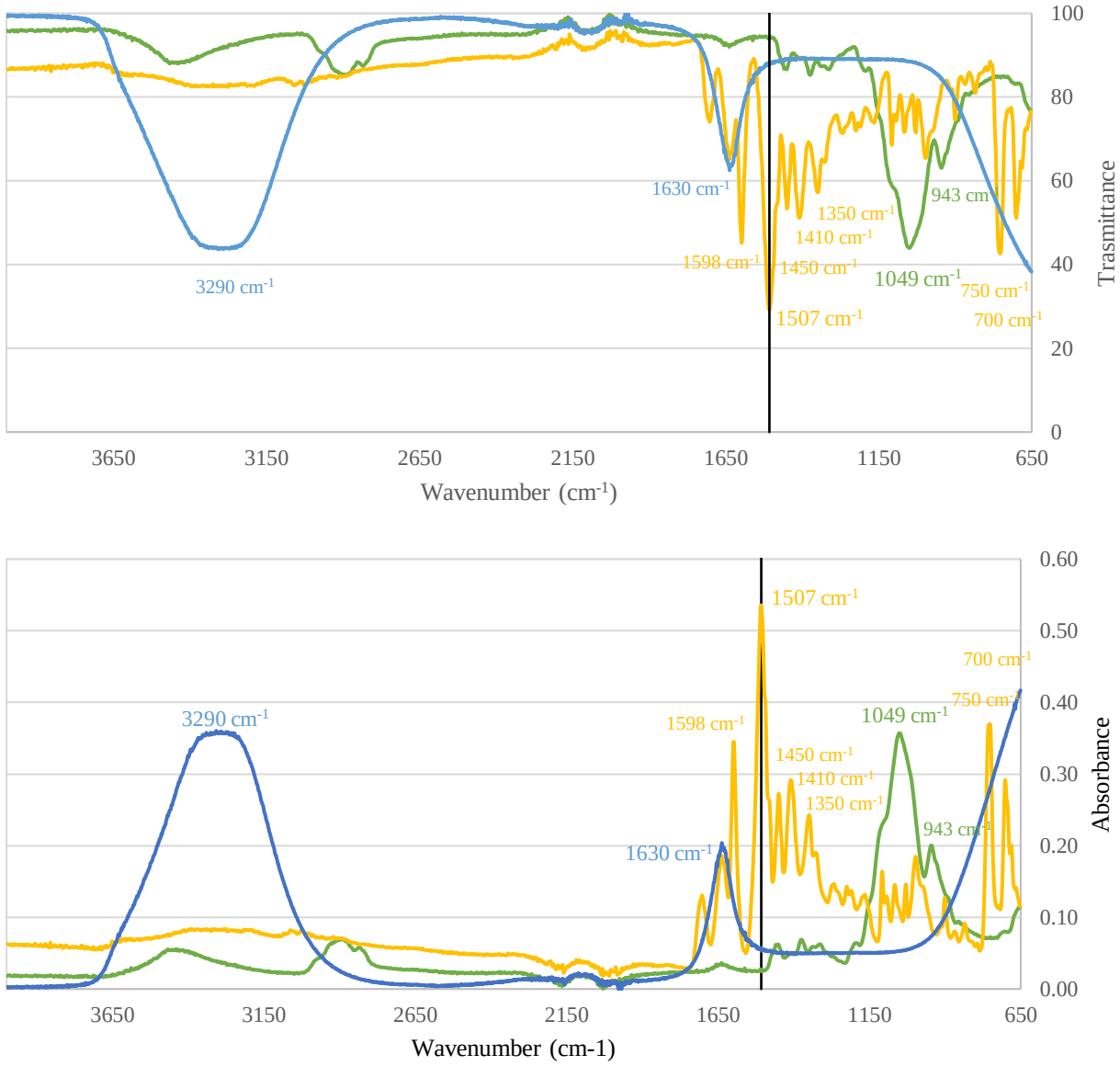


Figure III.20: IR spectrum of raw materials. Yellow line: Warfarin sodium, green line: Hypromellose and blue line: purified water. (Top)Transmittance, (bottom) Absorbance.

Finally, all raw materials were subjected to Raman spectroscopy (Figure III.21). Warfarin sodium showed a strong band at 1608 cm^{-1}, corresponding to the C-C stretching vibration. Also, at 1030 cm^{-1} and 1004 cm^{-1} the active substance shows two strong bands. In addition, Warfarin shows three strong bands at 1420 cm^{-1}, 1462 cm^{-1} and 1484 cm^{-1}. Finally, the band at 680 cm^{-1} can be attributed to the phenyl group of warfarin (Dimitrokalli et al., 2021; Sultan et al., 2020).

On the other hand, Hypromellose shows strong bands at 1368 cm^{-1} and at 1456 cm^{-1} attributed to the C-C stretching vibration (Adar, 2016; Fechner et al., 2010). Strong bands also appear at 1298 cm^{-1} and at the range 850-1174 cm^{-1}. Purified water does not show any strong bands at the measured region of 400-2300 cm^{-1}.

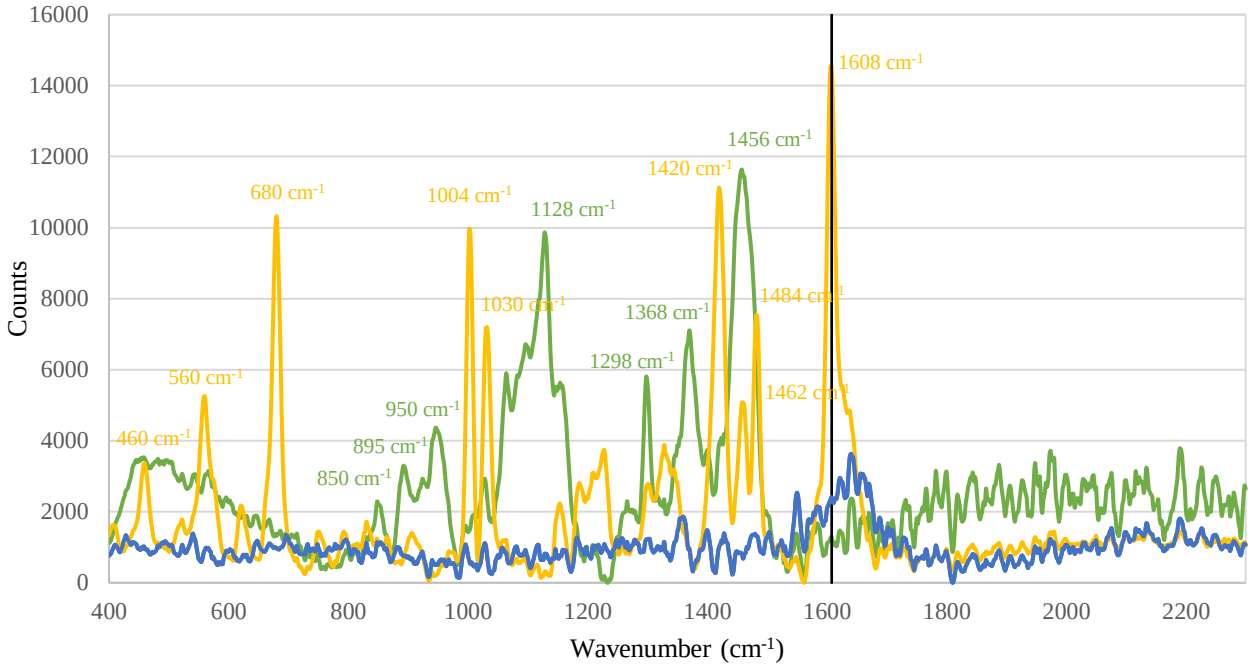


Figure III.21: Raman spectrum of raw materials. : Warfarin sodium, green line: Hypromellose and blue line: purified water.

Last but not least, Warfarin sodium and Hypromellose were subjected to stereoscopic and microscopic imaging in order to verify the solid state of the two raw materials. Warfarin sodium was purchased as an amorphous solid powder, while Methocel™ E4M in crystalline form. This was verified by the stereoscopic imaging of the raw materials as well as with the polarized imaging shown in Figure III.22 and Figure III.23 respectively. The polarized light revealed that only Methocel™ E4M exists in the crystalline form as its particle's fluorescence, while Warfarin sodium in the amorphous form.

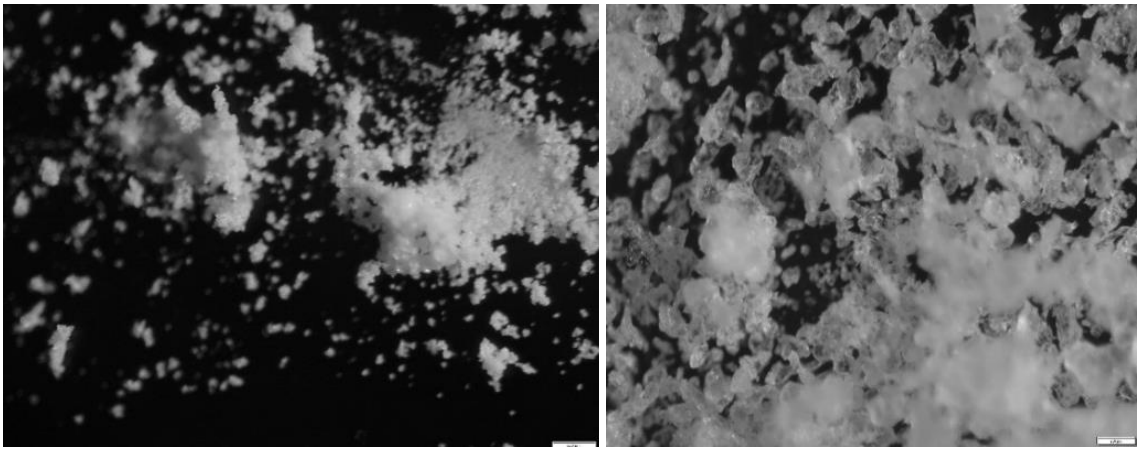


Figure III.22: (Left) Warfarin Sodium, (Right) Hypromellose - Methocel™ E4M (Stereoscope Olympus SC30, Japan).

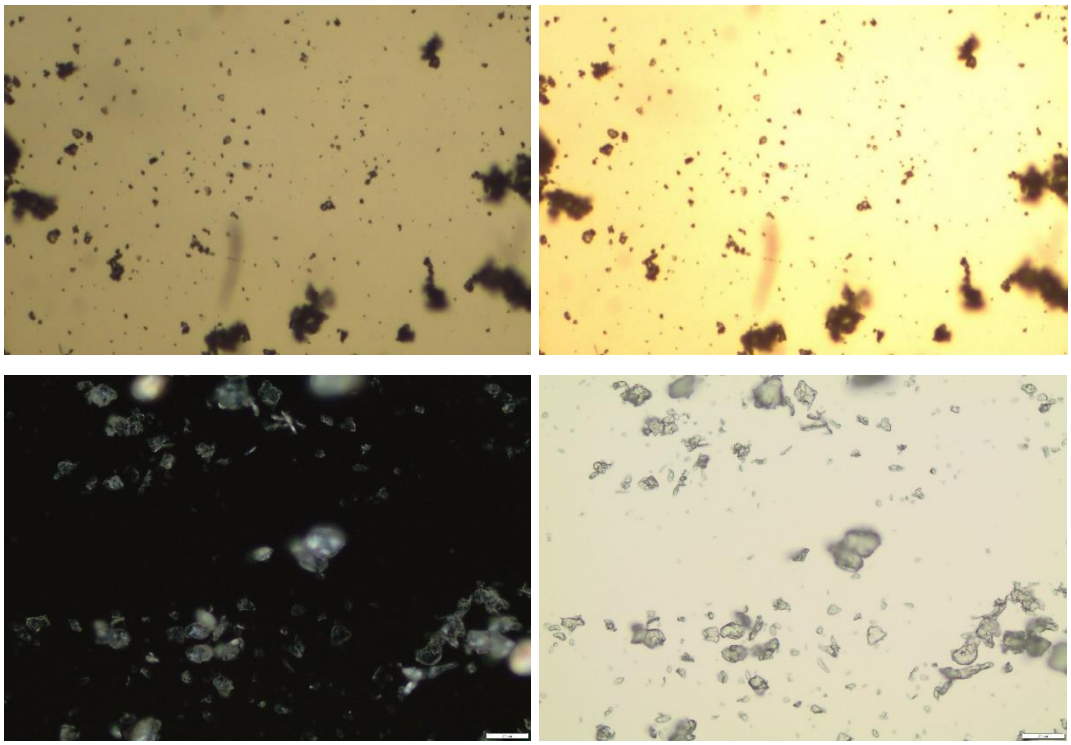


Figure III.23: (Top) Warfarin Sodium imaging and (bottom) Hypromellose - Methocel™ E4M with (left) and without (right) polarized light (Microscope Olympus BX41, Japan).

To conclude, all raw materials were able to be analyzed prior to use, firstly in terms of identification with three different analytical methods, UV/Vis, FT-IR, and Raman spectroscopy and secondly in terms of polymorphic form with the use of a stereoscope and a polarized microscope. All these techniques are easy to use, flexible, relatively cheap, and portable, providing reliable verification of the raw materials. Within the set-up of a hospital or a pharmacy, these techniques can be standard procedures prior to a compounding process.

Bulk gel Control

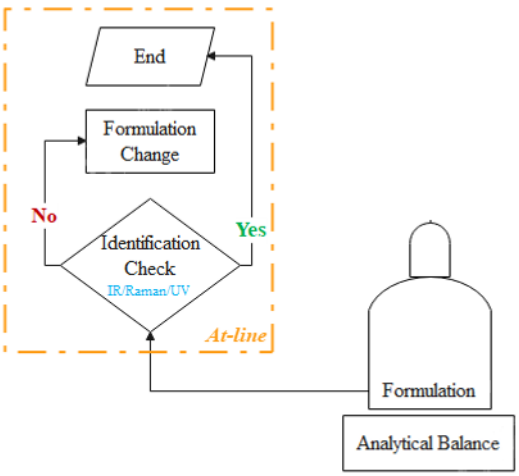


Figure III.24: Stage of Bulk gel identification.

An at-line process that can also be performed prior to the compounding process is the identification of the starting bulk material. In case that the formulation and process development of the final bulk solution has been successfully conducted by an approved supplier and is received in a sealed container by the pharmacy as a ready to use formulation, then this product can be tested on site for assuring its identity and %assay. This was performed by the same three analytical methods, namely UV/Vis, FT-IR, and Raman (Figure III.24).

Three different bulk gels were prepared with warfarin sodium content varying from 2.5% and 5.0% to 7.5% w/w. These were tested with the three analytical methods to verify their identity and API content. In terms of UV/Vis spectrophotometry, a certain amount of gel was dissolved in water and the absorbance at 308 nm was measured. The theoretical warfarin sodium concentration in the solution was compared to the calculated, measured concentration. The measurements revealed an absorbance at 308 nm as expected, and the %assay in good agreement with the theoretical values. The results are depicted in Table III.8. Thus, UV is a successful method for the fast identification and assay determination of the bulk gel solution. However, it requires an amount of gel to be subtracted from the closed container and be consumed in order to perform the measurements.

Table III.8: Identification and %assay results of Warfarin sodium bulk gel with UV/Vis spectrophotometry.

%w/w of Warfarin Sodium in Bulk gel	Identification of Warfarin Sodium at 308 nm	%Assay
2.5%	√	100.1% ± 0.78%
5.0%	√	99.4% ± 1.20%
7.5%	√	100.5% ± 2.04%

The second method tested for the identification and %assay of the bulk gel was FT-IR spectrometry. The three bulk gels with the different warfarin sodium content were measured and compared with standard reference solutions of known warfarin sodium concentration for the identification and assay determination. The results are depicted in Table III.9 and Figure III.25. It is worth mentioning that in higher warfarin sodium concentrations the assay determination is more accurate with less %RSD, which can be explained since the higher the concentration, the higher the FT-IR band, thus the signal to noise ratio is higher. Below certain concentration of Warfarin sodium (<1% w/w) in the bulk gel it was not possible to determine the API's characteristic bands, thus identification and %assay could not be performed. Nevertheless, this analytical method is also a successful method for the fast identification and assay determination of the bulk gel. It also requires a drop of gel to be subtracted from the closed container in order to perform the measurements.

Table III.9: Identification and %Assay results of Warfarin sodium bulk gel with IR spectrometry.

%w/w of Warfarin Sodium in Bulk gel	Identification of Warfarin Sodium at 1507 cm^{-1}	%Assay
2.5%	√	97.8% ± 1.54%
5.0%	√	101.3% ± 1.03%
7.5%	√	99.9% ± 0.62%

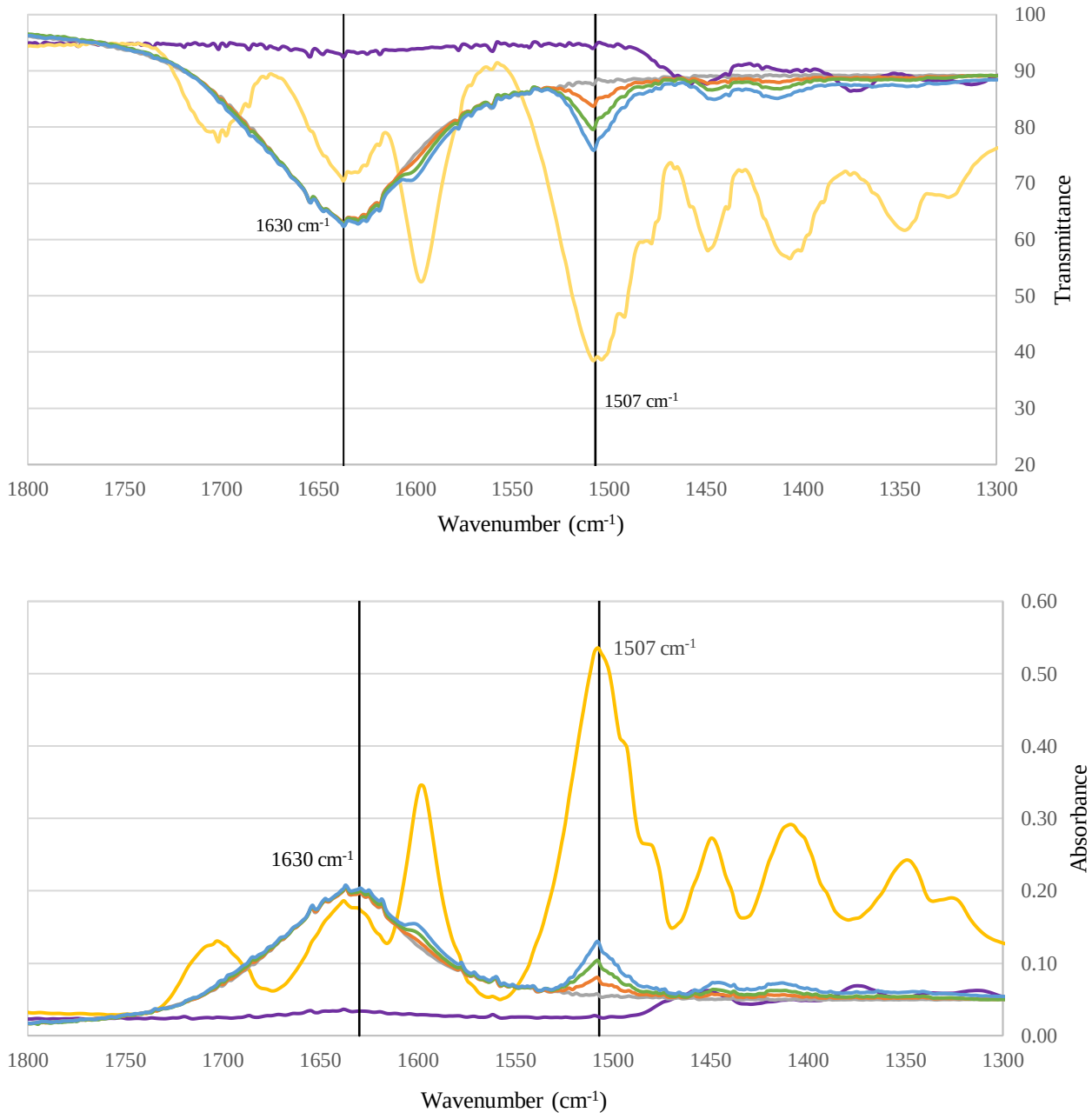


Figure III.25: IR spectrum of bulk gels. Orange line: 2.5% w/w Warfarin sodium gel, green line: 5.0% w/w Warfarin sodium gel, blue line: 7.5% w/w Warfarin sodium gel, yellow line: Warfarin sodium solid, purple line: Hypromellose solid and grey line: purified water. (Top) Transmittance and (Bottom) Absorbance.

Finally, Raman spectroscopy was used for the identification and assay determination of Warfarin sodium in the bulk gel. Some of the results are depicted in Figure III.26. In this case, as shown in the following figure, the identification of Warfarin sodium is successful in all concentrations in the bulk gel. However, the assay determination was not possible as there was no consistency in the intensity of the signal both at the samples with the same concentration and between the samples with different concentration. For example, in Figure III.26, the 7.5% w/w sample shows a lower signal in all strong bands of warfarin and especially at 1608 cm^{-1} than both 2.5% and 5.0% w/w samples. This phenomenon can possibly be explained

by the way the samples were measured, since they were contained in glass vials, resulting in distortion of light passing through glass walls inconsistently at each measurement. However, the same was observed with different types of containers, e.g., polypropylene plastic containers. Thus, Raman spectroscopy can be used only for the identification of the API and not for the assay determination. Nevertheless, in all gel concentrations the Raman spectrum for the API identification was identical in all bands with Warfarin sodium solid substance, providing high level of identification assurance.

Table III.10: Identification and %Assay results of Warfarin sodium with Raman spectrometry.

%w/w of Warfarin Sodium in Bulk gel	Identification of Warfarin Sodium at 1608 cm^{-1}	%Assay
2.5%	√	Not possible
5.0%	√	Not possible
7.5%	√	Not possible

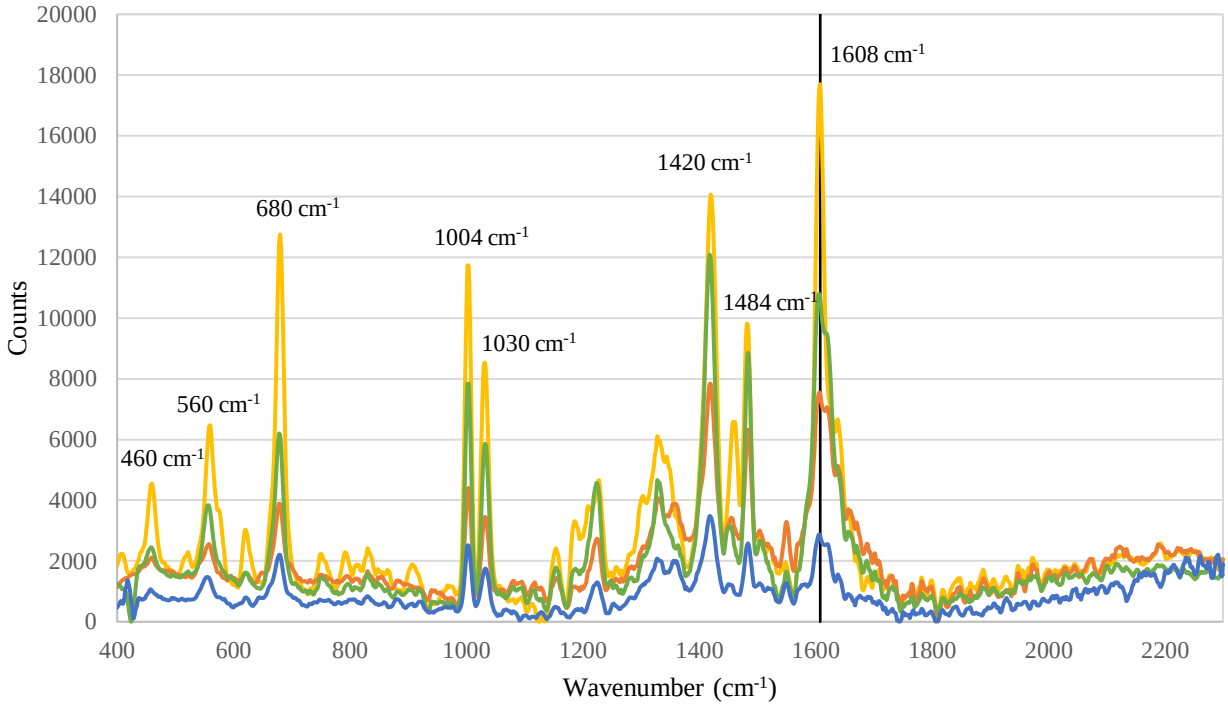


Figure III.26: Raman spectrum of bulk gels. Orange line: 2.5% w/w Warfarin sodium, green line: 5.0% w/w Warfarin sodium, blue line: 7.5% w/w Warfarin sodium and yellow line: Warfarin sodium solid substance.

In conclusion, at the stage of bulk gel characterization, it was possible to use UV/Vis spectrophotometry and FT-IR spectrometry for the identification and %assay determination of the API prior to the compounding process. Raman spectroscopy could be an alternative method, however, only for the identification of Warfarin sodium.

Wet film Control

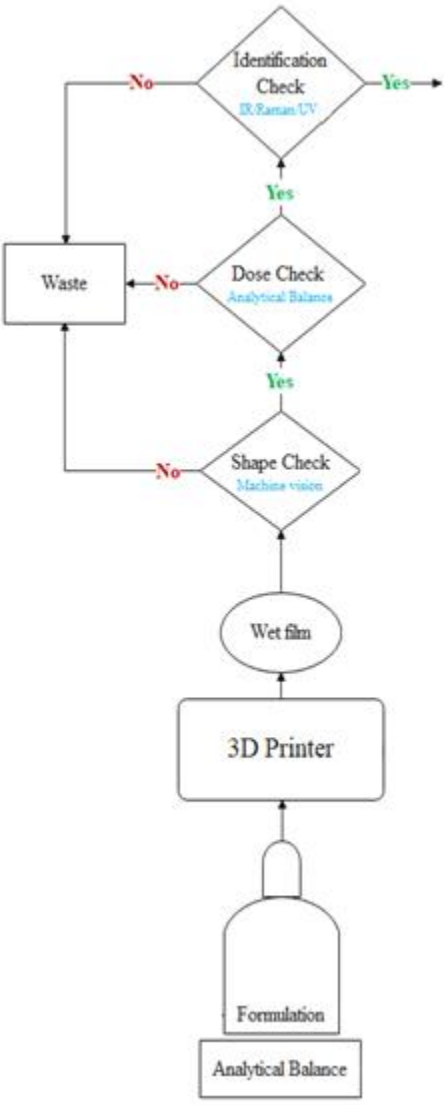


Figure III.27: 3D printing of wet film stage.

The next step of the system is the compounding process and the 3D print of the orodispersible films. At this point, the bulk gel is loaded to the semisolids print-head in order to produce the wet orodispersible films. The in-process controls that were performed at this step, in order to assure the quality of the printed film are dose check, appearance inspection and identification of the API. If one of these checks identifies a non-conforming film, then the films are rejected to waste (Figure III.27).

Initially, the produced films are checked through Machine Vision for defects. Possible defects during the printing process are bubbles, filling gaps, movement of the printing base resulting in distorted film shapes and/or dimensions, over-extrusion of material thus the shape and/or dimensions of the film are not accurate, and incomplete films due to finished material. Some examples of films with defects are shown in Figure III.28. From these defects, the three most probable to occur and selected for the neural network training

were incomplete films due to finished gel, bubbles due to trapped air in the gel and misshaped films due to misplacement/movement of the printing base.

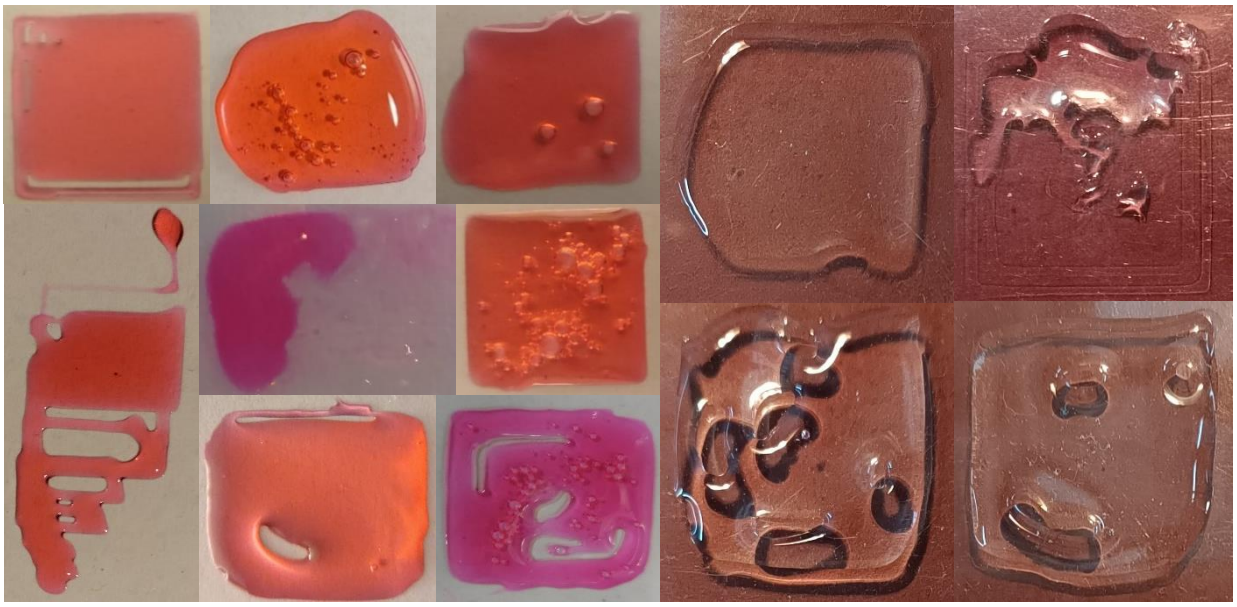


Figure III.28: (Left) Wet 3D printed orodispersible films with defects. For demonstration purposes red color was added in the film formulation. (Right) the most probable occurring defects during film printing.

The training and validation of the developed neural network resulted in a Machine Vision technique that was able to identify conforming and non-conforming films. These results could be obtained by training the system with only a limited number of pictures, such as 14 for "conforming" films and 15 for "non-conforming" films and by augmenting the data set. The output of the Machine Vision check is depicted in Figure III.29.

Figure III.29: Example of identification of defected films by machine vision.

Subsequently, the neural network was trained further to identify the type of defect that could occur during the printing process. The selected categories were named “Conforming”, “Type I Defect” (misplaced film), “Type II Defect” (finished gel) and “Type III Defect” (bubbles). Examples of the different categories are depicted in Figure III.30.

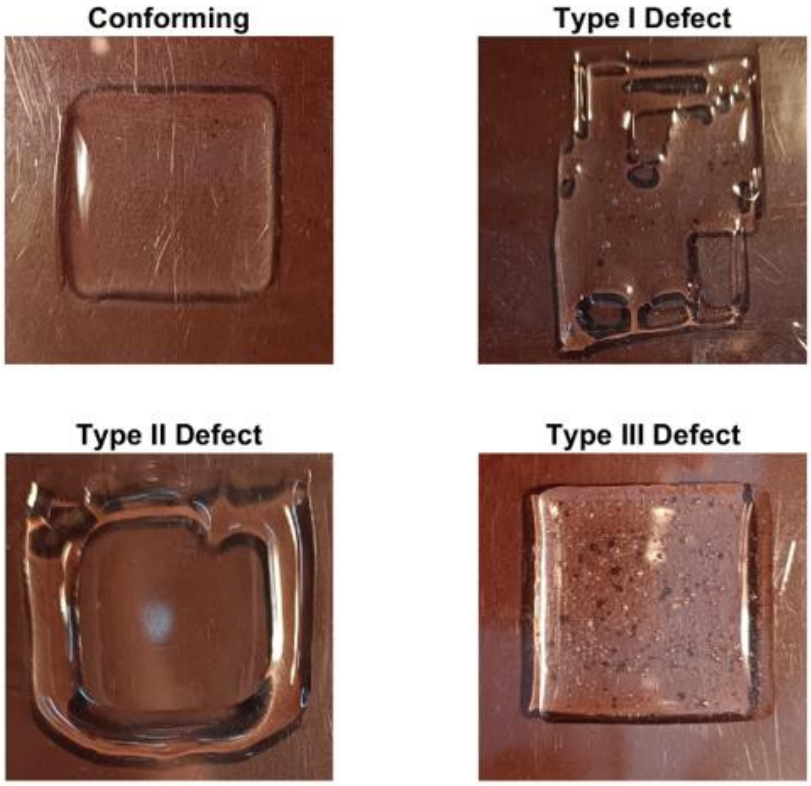


Figure III.30: Example of identification of defected films and defect categorization by machine vision.

Even though, neuron network was able to identify the type of defect, in same rare cases, the Type I and Type II defects could not be categorized correctly and were “mistaken” with each other. This happened due to the fact that the misplaced films may differ from each other to a great degree and additionally, some misplaced films could be mistaken for finished gel even by a human. Therefore, this is an objectively difficult problem to solve, which is related to exactly which samples (which can differ greatly) end up in the training and testing sets.

In order to solve the above problem and be able to categorize the different defects, the process followed was first of all to train 10 neurons, each time randomly dividing the dataset into individual training/validation/testing sets. The second step was to analyze their overall performance, comment on the effect of hyperparameters and finally discuss the occurrence of false positives/negatives. For implementation, the best neural network will be chosen, but this is of the least importance compared to the investigation on the general applicability of the method.

In more detail, ten neuron networks were trained (10 "runs"). The set of 130 samples was divided into 90/20/20 for training/validation/testing respectively. This corresponds to the standard 70%/15%/15% with slight rounding. In terms of the hyperparameters, the min-batch size was set to 30 in order to separate the whole data set to the training/validation/testing without excluding any samples (30 is a divisor of 90, so a

sample is never excluded). For the max epochs, a large upper limit of 20 was set, because the following stopping criterion was used: "*ValidationPatience specifies the number of times that the loss on the validation set can be larger than or equal to the previously smallest loss before network training stops.*". The neuron network was trained with the ValidationPatience set to two different levels, 3 little patience or 5 enough patience to see the dependency. The only other critical hyperparameter left is the learning rate. This was set to 1e-3 corresponding to large or fast learning rate of the neuron or to 1e-4 corresponding to small or slow learning rate.

The results for ten runs and three different hyperparameter combinations are depicted in the following tables (Table III.11-Table III.13).

Table III.11: Results for the Neural network with fast learning rate (se to 1e-3) and little patience (set to 3).

Predicted Label	Correct Label	Run Number	Validation Accuracy	Testing Accuracy	Comments
Type I Defect (Misplaced)	Conforming	1	95%	90%	False Negative
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	1	95%	90%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	2	85%	90%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	2	85%	90%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	3	95%	95%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	4	95%	95%	
NO ERRORS	NO ERRORS	5	100%	100%	
Conforming	Type I Defect (Misplaced)	6	100%	85%	False Positive
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	6	100%	85%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	6	100%	85%	
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	7	95%	95%	
Type III Defect (Bubbles)	Conforming	8	60%	70%	
Conforming	Type I Defect (Misplaced)	8	60%	70%	False Positive
Type III Defect (Bubbles)	Type I Defect (Misplaced)	8	60%	70%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	8	60%	70%	
Type III Defect (Bubbles)	Type II Defect (Finished Gel)	8	60%	70%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	8	60%	70%	
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	9	95%	90%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	9	95%	90%	

Predicted Label	Correct Label	Run Number	Validation Accuracy	Testing Accuracy	Comments
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	10	85%	85%	
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	10	85%	85%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	10	85%	85%	
		Means:	**90.5%**	**89.5%**	

Table III.12: Results for the Neural network with fast learning rate (se to 1e-3) and enough patience (set to 5).

Predicted Label	Correct Label	Run Number	Validation Accuracy	Testing Accuracy	Comments
Type I Defect (Misplaced)	Conforming	1	75%	80%	False Negative
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	1	75%	80%	
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	1	75%	80%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	1	75%	80%	
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	2	90%	95%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	3	95%	85%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	3	95%	85%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	3	95%	85%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	4	95%	95%	
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	5	95%	95%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	6	90%	95%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	7	85%	85%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	7	85%	85%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	7	85%	85%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	8	100%	95%	
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	9	90%	95%	
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	10	95%	95%	
		Means:	**91%**	**91.5%**	

Table III.13: Results for the Neural network with slow learning rate (se to 1e-4) and enough patience (set to 5).

Predicted Label	Correct Label	Run Number	Validation Accuracy	Testing Accuracy
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	1	90%	90%
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	1	90%	90%
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	2	85%	95%
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	3	80%	90%
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	3	80%	90%
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	4	100%	95%
NO ERRORS	NO ERRORS	5	100%	100%
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	6	90%	90%
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	6	90%	90%
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	7	95%	85%
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	7	95%	85%
Type I Defect (Misplaced)	Type II Defect (Finished Gel)	7	95%	85%
NO ERRORS	NO ERRORS	8	100%	100%
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	9	95%	90%
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	9	95%	90%
Type II Defect (Finished Gel)	Type I Defect (Misplaced)	10	100%	95%
		Means:	**93.5%**	**93.0%**

The above results reveal that as expected, the small learning rate and enough patience give the best results. The main focus is to have 100% error recognition. It is acceptable for the neuron to "confuse" the two disputed types of error, but it is not acceptable to have false negatives and, worse, false positives. Even though in all tested cases the overall mean accuracy of recognizing the type of defect was around 90%, in the case of fast learning rate and little patience, the results revealed one false negative and two false positives, while in the case of fast learning rate and enough patience, there was only one case of false negative, without false positives. However, in the case of slow learning rate and enough patience, there was 100% error recognition accuracy without false positives or negatives.

It was expected in advance that the slow learning rate and enough patience would produce the best results, however, the tradeoff is computational resources and training time. The suboptimal combinations presented

show the course of development of the training of the neuron networks and to present the risks of a positive and false negative. An example of the training process of a neural network is depicted in Figure III.31.

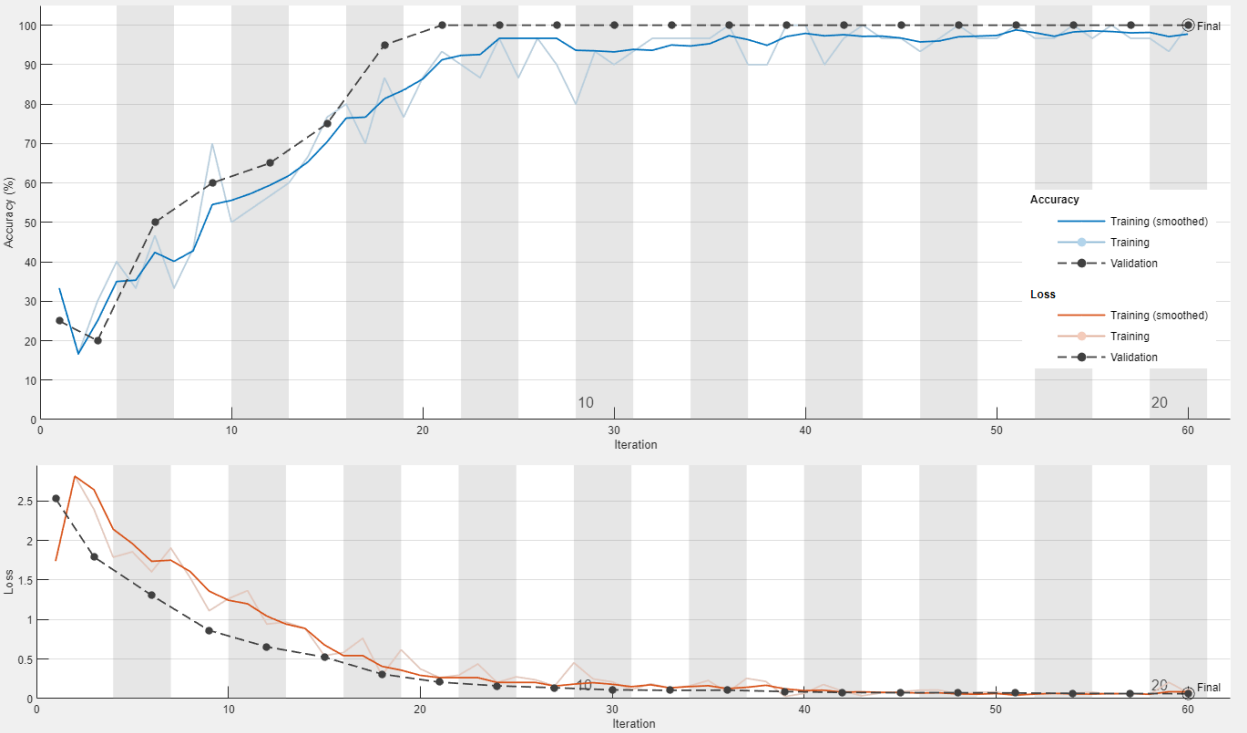


Figure III.31: Example of the training process of a neural network.

Because we are interested in not having false positives or negatives, we find sets of parameters that on average lead to:

- 100% error recognition
- 93% exactly correct class recognition
- 0% false positives or negatives

Thus, in the vast majority of all cases, the neuron network can recognize if there is a defect in the printed film and furthermore can categorize the defect. In the very small chance that it is wrong, it simply mistakes the two types of defects together, which is trivial and with very little harm to the final outcome. The main focus is not to have defected films ending up to the patient, which cannot be the case with the implementation of the machine vision control.

The neural network implemented to the developed system could be one of the neurals with 100% accuracy, such as No. 5 or No.8 with the best hyperparameters i.e., slow learning rate (se to 1e-4) and enough patience (set to 5).

Examples of the outcome of a poorly trained neural network and the neural network No. 5 with 100% accuracy, are depicted in the following figures (Figure III.32 and Figure III.33).

Prediction: Conforming
Correct Prediction

Prediction: Type II Defect
True label: Conforming
False Negative

Prediction: Conforming
Correct Prediction

Prediction: Type II Defect
True label: Type I Defect
Trivial Error

Prediction: Type I Defect
Correct Prediction

Prediction: Type I Defect
Correct Prediction

Prediction: Conforming
Correct Prediction

Prediction: Conforming
Correct Prediction

Prediction: Conforming
True label: Type I Defect
False Positive

Prediction: Type I Defect
Correct Prediction

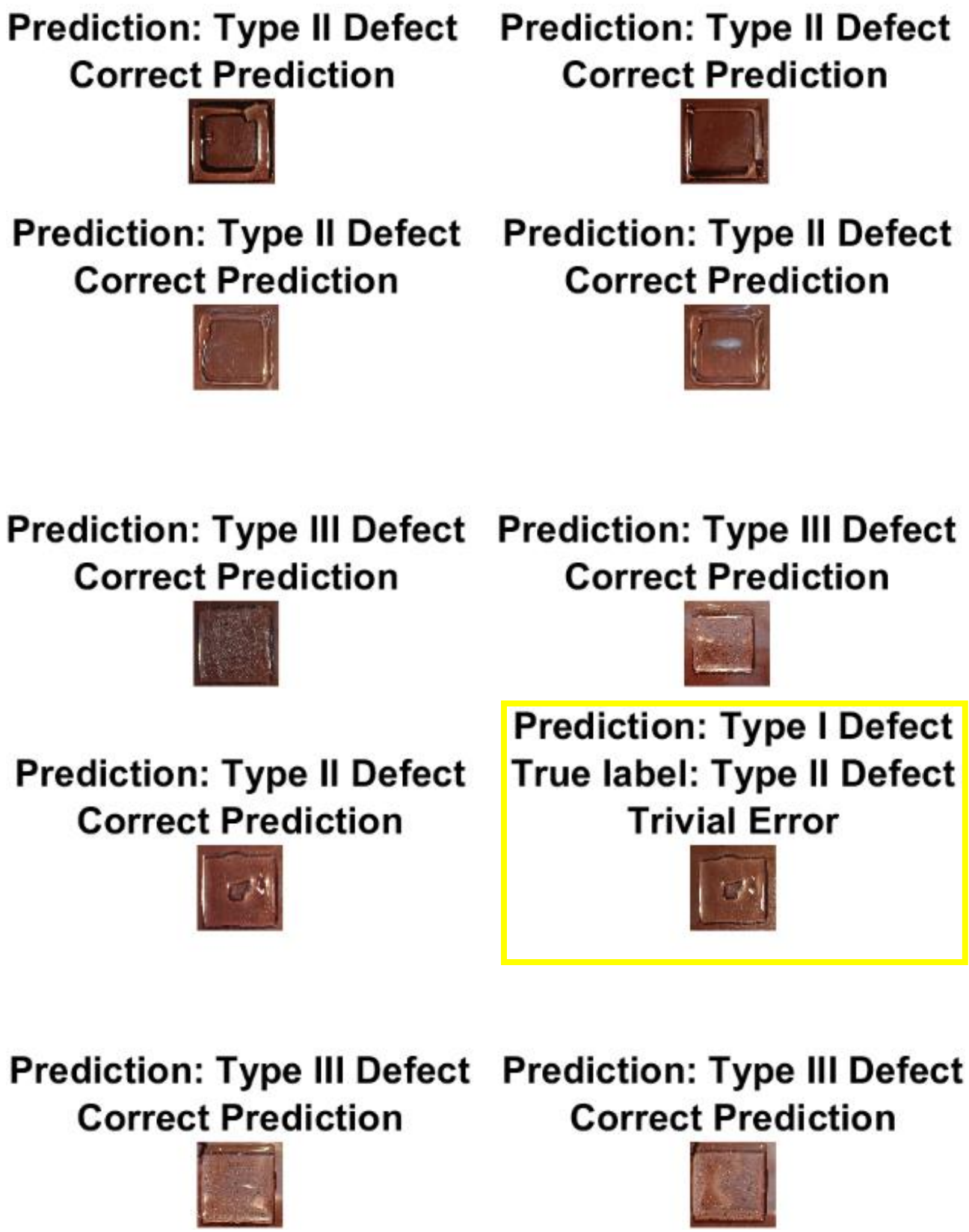


Figure III.32: Example of the outcome of a poorly trained neural network with all possible errors. The false negative or false positive predictions are depicted with a red frame, while the trivial errors with yellow frame.

Prediction: Conforming
Correct Prediction

Prediction: Conforming
Correct Prediction

Prediction: Conforming
Correct Prediction

Prediction: Type I Defect
Correct Prediction

Prediction: Type I Defect
Correct Prediction

Prediction: Type I Defect
Correct Prediction

Prediction: Conforming
Correct Prediction

Prediction: Conforming
Correct Prediction

Prediction: Type I Defect
Correct Prediction

Prediction: Type I Defect
Correct Prediction

Prediction: Type II Defect
Correct Prediction

Prediction: Type II Defect
Correct Prediction

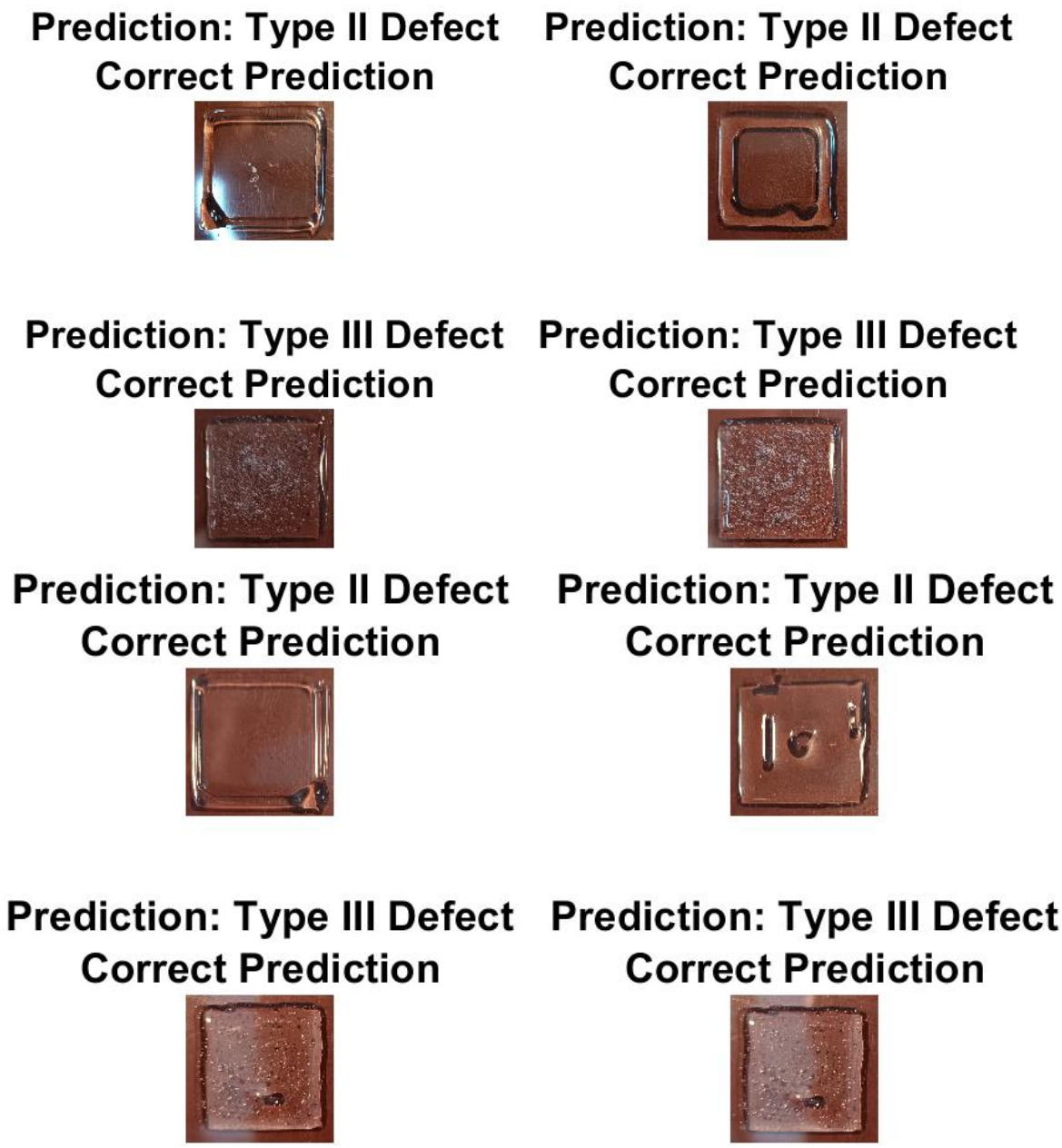


Figure III.33: Example of the outcome of No. 5 neuron network, a highly trained neural network with 100% prediction accuracy.

All in all, with a limited number of pictures, thus a small data set, a neural network could be developed that was able to not only identify "conforming" and "not-conforming" produced films but also categorize the type of defect with 100% accuracy. Thus, during a production batch, a picture can provide the information of a successful or a non-successful production and point out the reason of failure, if any.

The second in-process control performed at the wed 3D printed films is the dose check. Since the formulation of the films is known, through a simple weighing at an analytical balance, the exact dose of Warfarin sodium in the particular 3D printed film can be calculated. For the three different bulk gels and the two film sizes, the average weight was measured and is depicted in Table III.14.

Table III.14: Average weight values of wet 3D printed orodispersible films; mean value ± SD (n = 20).

Wet Film	Weight (mg)	Wet Film	Weight (mg)
15x15mm from gel 2.5% w/w Warfarin sodium	252.11 ± 33.02	25x25mm from gel 2.5% w/w Warfarin sodium	699.29 ± 17.10
15x15mm from gel 5.0% w/w Warfarin sodium	247.78 ± 31.78	25x25mm from gel 5.0% w/w Warfarin sodium	697.50 ± 25.86
15x15mm from gel 7.5% w/w Warfarin sodium	261.25 ± 14.52	25x25mm from gel 7.5% w/w Warfarin sodium	709.00 ± 20.71
Average	253.71	Average	701.93
SD	5.62	SD	5.05
%RSD	2.21	%RSD	0.72

Regardless the API content in the film, the average weight for the 15x15mm square film is 254 mg, while for the 25x25mm film is 702 mg. Depending on the gel content of Warfarin sodium, the dose in each film varies. However, in any case the %RSD will result in dose difference of less than 1 mg. The accuracy of the %assay in each film was verified by %assay determination in the dry film by dissolving either the whole film or parts of it and measuring its content via UV/Vis spectrophotometry. All results reviled close agreement of the dose determination through weighing of the wet film and the practical measurements. These results are presented in the following section.

Finally, the last control performed during this stage of compounding is the identification of the API. However, none of the chosen analytical methods was able to identify Warfarin sodium (Table III.15). UV/Vis was not possible to be performed since it is a destructive method that requires the dissolution of the film. FT-IR and Raman spectroscopy were tested, however since they require for the sample to be positioned in a specific spot for the light beam to target the wet film, the resulted spectrums did not provide clear and reproducible API identification.

Table III.15: In-process controls at the compounding stage of wet film.

%w/w of Warfarin Sodium in wet film	Film shape check	Film dose Check	Identification of Warfarin Sodium
2.5%	√	√	Not possible
5.0%	√	√	Not possible
7.5%	√	√	Not possible

Dry film Control

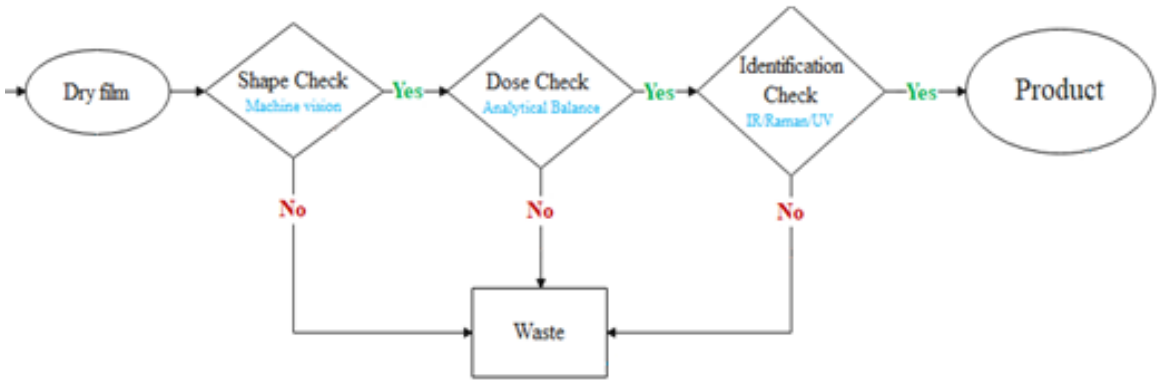


Figure III.34: Dry film control stage.

The 3D printed wet films were left to room temperature to dry until stable weight. The dry films were then checked in terms of defects, dose, and API identification (Figure III.34). As in the case of the wet films, a similar machine vision system could have been used to identify defected films, however a new Deep Neural Network based Machine Vision system was not developed and the films were checked visually. In the event that the dried films were not conforming, they were rejected. Some examples of films with defects are shown in Figure III.35. Red color was added in the film formulation for better demonstration.

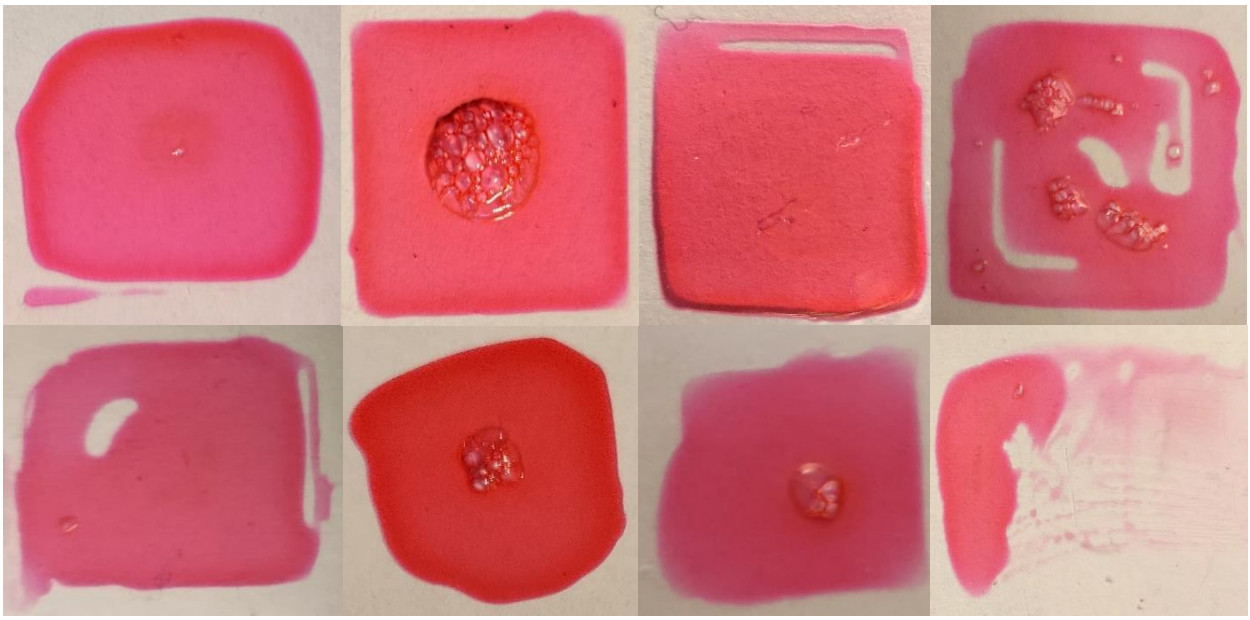


Figure III.35: Dry 3D printed orodispersible films with defects. For demonstration purposes red color was added in the film formulation.

The second in-process control performed was the dose check. The dry films produced by the three different bulk gels and for the two different sizes were weighted and their measurements are depicted in Table III.16. Also, the films were characterized in terms of thickness. It was observed that the increase in the %w/w API content in both film sizes results in higher average film weight. This was expected as in the gel formulation the %w/w of Hypromellose remains constant, water evaporates and the only constituent that varies is Warfarin sodium. Thus, it was expected that when increasing the API content by two-fold or three-fold, the

total film weight would double and triple respectively. However, even though an increase is observed, the total weight is not doubled or tripled when twice or three times the quantity of API is added. Finally, an increase in the film thickness is observed when increasing the content of warfarin sodium in both film sizes. Also, the film thickness is comparable in each API content regardless the film size.

Table III.16: Average weight and thickness values of dry 3D printed orodispersible films; mean value ± SD (n = 20).

Dry Film 15x15mm	Weight (mg)	Thickness (mm)	Dry Film 25x25mm	Weight (mg)	Thickness (mm)
from gel 2.5% w/w Warfarin sodium	15.63 ± 0.57	0.0646 ± 0.0120	from gel 2.5% w/w Warfarin sodium	39.87 ± 0.55	0.0629 ± 0.0035
from gel 5.0% w/w Warfarin sodium	23.50 ± 0.96	0.0807 ± 0.0004	from gel 5.0% w/w Warfarin sodium	58.12 ± 1.52	0.0882 ± 0.0137
from gel 7.5% w/w Warfarin sodium	28.20 ± 1.77	0.1181 ± 0.0129	from gel 7.5% w/w Warfarin sodium	77.04 ± 0.94	0.1230 ± 0.0022

In this process stage, to verify the accuracy of the %assay in each film and the repeatability of the production process, the %assay was determined in the dry film by dissolving either the whole film or parts of it and measuring its content via UV/Vis spectrophotometry. The parts of the films that were measured are shown in Figure III.36: Sampling way for %assay determination in the 3D printed orodispersible films. (Left) whole film, (middle) division of film in two equal parts vertically, (right) division of film in two parts, the inner/center part, and the outer part. For demonstration purposes red color was added in the film formulation.Figure III.36 and the assay results are presented in the following table.

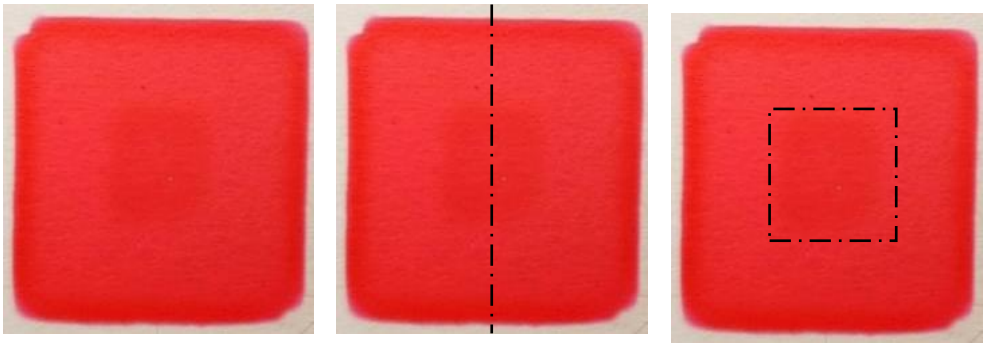


Figure III.36: Sampling way for %assay determination in the 3D printed orodispersible films. (Left) whole film, (middle) division of film in two equal parts vertically, (right) division of film in two parts, the inner/center part, and the outer part. For demonstration purposes red color was added in the film formulation.

Either the whole film was dissolved in specific amount of water to determine the %assay or each film was divided in two parts and the %assay in each part was measured. In one case, the film was divided vertically in two half parts and in the second case the center part of the film was separated from the outer part.

Table III.17: %Assay of 3D printed orodispersible films; mean value ± SD (n = 3).

	Film 15x15mm	%Assay	Film 25x25mm	%Assay
Film from gel 2.5% w/w Warfarin sodium	Whole film	102.8% ± 1.66%	Whole film	100.7% ± 1.40%
	Center part	109.6% ± 4.20%	Center part of film	109.0% ± 3.00%
	Outer part	100.6% ± 1.18%	Outer part of film	96.0% ± 2.50%
	Half part	103.0% ± 2.67%	Half part	102.6 ± 1.05%%
	Half part	104.7% ± 2.85%	Half part	99.7% ± 1.25%
Film from gel 5.0% w/w Warfarin sodium	Whole film	100.3% ± 0.49%	Whole film	101.9% ± 0.49%
	Center part	104.8% ± 3.27%	Center part	105.6% ± 3.53%
	Outer part	99.2% ± 2.86%	Outer part	101.3% ± 3.25%
	Half part	104.5% ± 1.32%	Half part	102.6% ± 1.07%
	Half part	104.6% ± 3.10%	Half part	101.6% ± 1.33%
Film from gel 7.5% w/w Warfarin sodium	Whole film	102.4% ± 0.40%	Whole film	100.1% ± 1.37%
	Center part	99.2% ± 1.35%	Center part	101.2% ± 0.96%
	Outer part	102.4% ± 2.05%	Outer part	101.6% ± 1.03%
	Half part	99.5% ± 0.76%	Half part	99.7% ± 2.10%
	Half part	102.8% ± 1.06%	Half part	103.1% ± 2.08%

The %assay measurements (Table III.17) revealed that regardless the film size or the API content, when measuring the whole film, there is close agreement between the theoretical values calculated by weighing the 3D printed films and the practical measured %assay values with UV/Vis. Furthermore, it was observed that in some cases, there was non-uniformity between the subparts of the film. This was more obvious between the center and the outer part of the film compared to the vertical half parts. This might be explained by the way the film dries, from the outer part to the inner part, resulting in more solid content in the center of the film. Also, the surface that the films were left to dry might have a small inclination, resulting in more material in one side compared to the other half side.

Nevertheless, this in-process control can provide information regarding the dose accuracy in the 3D printed film as well as the identification of the active ingredient. Regarding the dimensions, weight, thickness and %assay in the whole film (Table III.17 & Table III.18), it was demonstrated that the printing process is capable of preparing reproducible films of the same quality.

Table III.18: Identification and %Assay results of Warfarin sodium in dry films with UV spectrophotometry.

Identification of Warfarin Sodium with UV/Vis at 308 nm	%Assay determination of Warfarin Sodium with UV/Vis at 308 nm
√	√
√	√
√	√

Finally, apart from the UV/Vis analytical method, both FT-IR and Raman spectroscopy were tested for the in-process control of warfarin sodium identification in the dry film. The results are depicted in the following figures (Figure III.37-Figure III.38). In terms of FT-IR spectroscopy, in all films regardless the API content or size the constituents could be identified. In the dry films, the bands attributed to water, Hypromellose or

warfarin sodium were obvious both with the use of transmittance or absorbance, as depicted in Figure III.37. The characteristic band of warfarin sodium at 1507 cm^{-1} was visible in all films. Additionally, the Hypromellose band at 1049 cm^{-1} and at around 2900 cm^{-1} are also present in all films. At 1637 cm^{-1} a band is also present that can be attributed to both warfarin sodium and water as these bands overlap with each other. Finally, at the range 3370-3250 cm^{-1} at which the strong band of water appears, all films show a low intensity band, which might be due to the water content left in the film after drying.

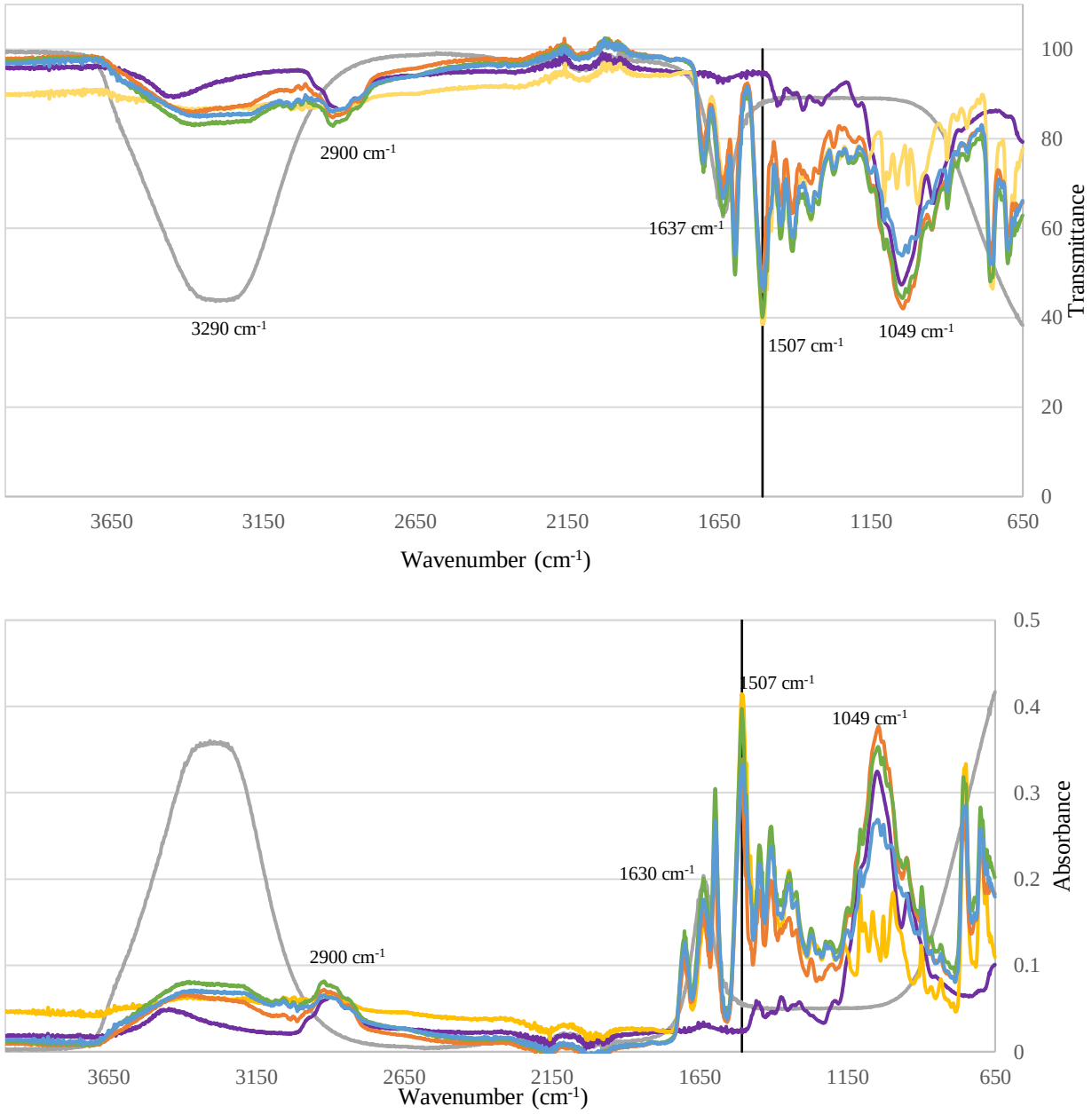


Figure III.37: IR spectrum of dry films. Orange line: film from 2.5% gel, green line: film from 5% gel, blue line: film from 7.5% gel, yellow line: Warfarin sodium solid substance and purple line: Hypromellose solid. (Top) Transmittance, (Bottom) Absorbance.

A magnification of the IR spectrum at the range 1850-650 cm^{-1} reveals in more detail the bands attributed to each constituent of the formulation. The bands that can be attributed to warfarin sodium are at 1700 cm^{-1}, 1598 cm^{-1}, 1507 cm^{-1}, 900 cm^{-1}, 750 cm^{-1} and 700 cm^{-1}. The characteristic bands of Hypromellose are at 1049 cm^{-1} and 943 cm^{-1}. The bands at 1450 cm^{-1}, 1410 cm^{-1}, 1350 cm^{-1} and 1340 cm^{-1} could probably be attributed to the API, however, Hypromellose also shows some weaker bands at that area that could also contribute. At the area of 1160-900 cm^{-1}, where the main peak of Hypromellose is obvious, warfarin sodium also shows transmittance. Thus, in all film samples at that area, "shoulders" of warfarin sodium are obvious in the main band at 1049 cm^{-1}. Finally, the band at 1630 cm^{-1} obvious in all film samples, judging from the shape of the peak, could probably attributed to the API and not the water.

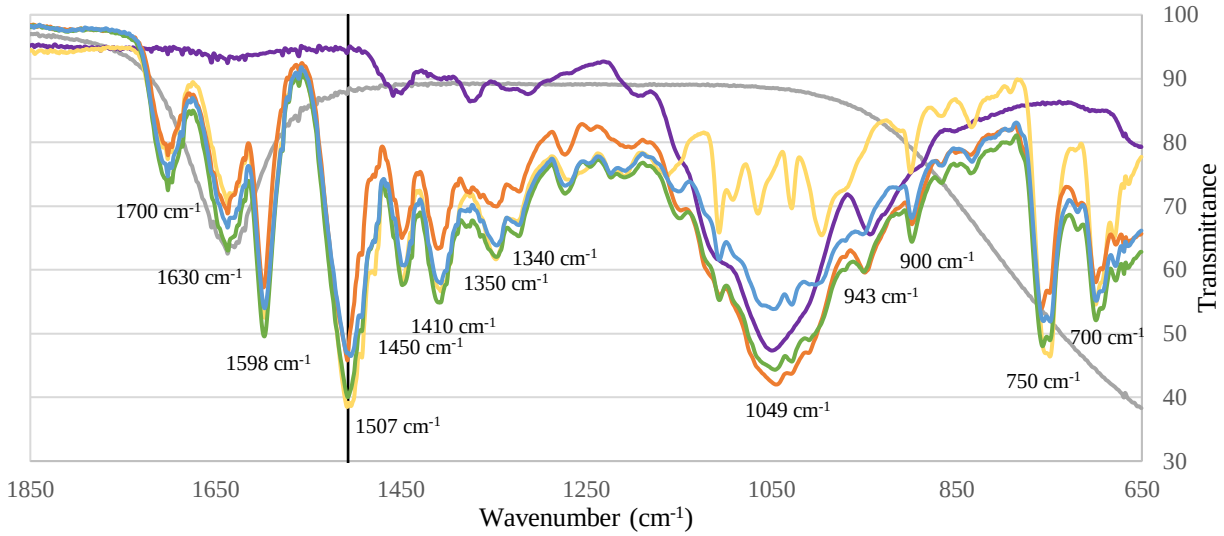


Figure III.38: Transmittance IR spectrum of dry films magnification at the range 1850-650 cm^{-1}. Orange line: film from 2.5% gel, green line: film from 5% gel, blue line: film from 7.5% gel, yellow line: Warfarin sodium solid substance and purple line: Hypromellose solid.

In conclusion, FT-IR spectroscopy is a useful tool for the identification of the constituents of the dry film and could be used as an in-process quality control method to ensure that the produced final product is of ensured quality. However, as depicted in the above figures, there is no consistency in the absorbance/transmittance intensity in respect to the API content in the films. For example, the film with the highest amount of warfarin sodium shows less transmittance than the film with the lowest warfarin sodium amount. This was obvious not only when compared films with different API content but also within measurement of the same film. Thus, this analytical method cannot be used for the %assay determination in the produced films. Nevertheless, the identification of the API is possible with a high degree of confidence (Table III.19).

Table III.19: Identification and %Assay results of Warfarin sodium in dry films with IR spectrometry.

Identification of Warfarin Sodium with IR at 1507 cm^{-1}	**%Assay determination of Warfarin Sodium with IR at 1507 cm^{-1}**
√	X
√	X
√	X

Since the %assay determination in the dry films was not possible with FT-IR spectroscopy, an alternative method apart from UV/Vis was investigated. As the qualitative and quantitative determination of the API was possible to the bulk gels via FT-IR spectroscopy, it was worth trying to dissolve the films and evaluate the production process and the final product in terms of warfarin sodium content using FT-IR spectroscopy in the solutions. Thus, depending on the size and API amount, each film was dissolved in a defined water quantity and measured via FT-IR spectroscopy. Standard solutions of warfarin sodium were prepared in various concentrations, ranging from 0.005 mg/ml to 10 mg/ml, in order to quantify the dissolved films. The assay results were compared to the results obtained from the UV/Vis spectrophotometry that was performed in the same solutions. Examples of the obtained results is depicted in Table III.20.

Table III.20: %Assay determination of Warfarin sodium in dissolved films with IR spectrometry vs UV/Vis spectrophotometry.

Warfarin amount in film (mg)	**Dilution 1 (mg/ml)**	**Dilution 2 (mg/ml)**	**Dilution 3 (mg/ml)**	**%Assay determination of Warfarin Sodium with UV/Vis at 308 nm**	**%Assay determination of Warfarin Sodium with FT-IR at 1507 cm^{-1}**
7.036	1.407	0.141	0.012	100.03%	81.2% - 103.1%
18.001	1.800	0.180	0.015	100.30%	95.3% - 105.7%
36.117	7.223	0.072	0.015	99.61%	93.9% - 99.8%

Depending on the warfarin sodium initial content in the film and the degree of dilution, thus the final concentration in the solution, the %assay determination varied. For example, a film with low initial amount of API e.g., 7.036 mg, that was dissolved in a high volume giving a final concentration of 0.012 mg/ml, when determined with FT-IR absorbance would result in an %assay of 81.2%. On the other hand, the same film if dissolved at a final concentration of 1.407 mg/ml would result in %assay of 103.1% (Figure III.39). This was observed in the films with higher amount of warfarin sodium but the %assay range was narrower. Thus, the higher the initial API amount in the film and the lower the dilution would result in less deviation in the %assay determination. In conclusion, this method could be an alternative tool apart from the qualitative determination of the API in the final product, also an additional quantitative tool. However, when compared to the UV/Vis analytical method, FT-IR it is less accurate. Nevertheless, FT-IR it is small and portable equipment which requires less amount of sample and can be integrated easily in the set-up of a hospital pharmacy.

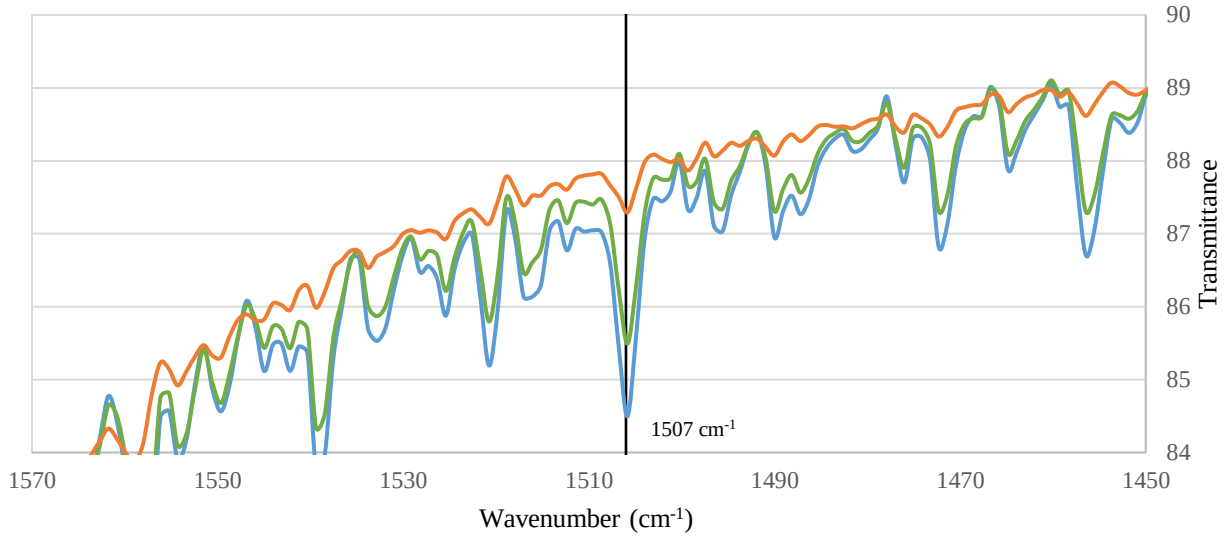


Figure III.39: Transmittance IR spectrum of dissolved films magnification at the range 1570-1450 cm^{-1}. Orange line: 0.012 mg/ml warfarin sodium, green line: 0.141 mg/ml warfarin sodium and blue line: 1.407 mg/ml warfarin sodium.

In terms of Raman spectrometry, it was possible to identify in the film both warfarin sodium and Hypromellose. In the Raman spectra of the films with the different concentrations, some bands can be attributed to warfarin sodium and some to Hypromellose. As depicted in Figure III.40, the basic band at 1608 cm^{-1} can clearly be attributed to warfarin sodium. Other, bands at 460 cm^{-1}, 560 cm^{-1}, 680 cm^{-1}, 1004 cm^{-1}, 1030 cm^{-1}, 1228 cm^{-1}, 1420 cm^{-1}, 1462 cm^{-1} and 1484 cm^{-1} also belong to warfarin sodium. On the other hand, the bands at 1128 cm^{-1} and 1298 cm^{-1} are representative for Hypromellose.

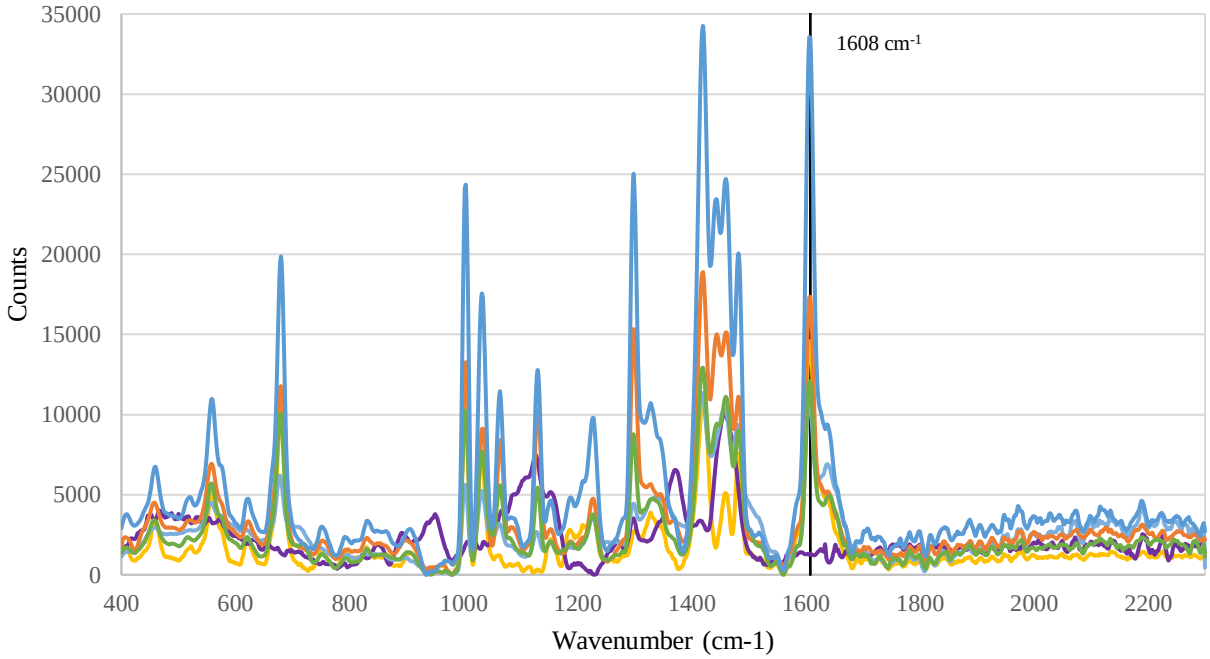
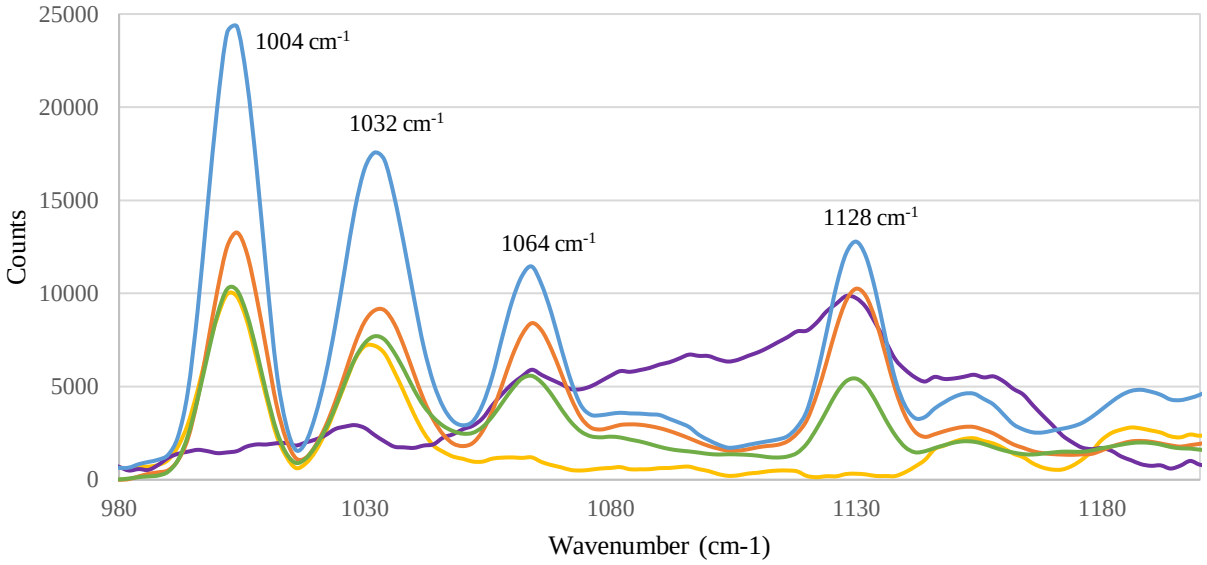


Figure III.40: Raman spectrum of dry films. Orange line: film from 2.5% gel, green line: film from 5% gel, blue line: film from 7.5% gel, yellow line: Warfarin sodium solid substance and purple line: Hypromellose solid.

At the area of 980-1200 cm^{-1}, four major bands are obvious as depicted in the top Figure III.41. The two bands at 1004 cm^{-1} and at 1032 cm^{-1}, can be attributed at warfarin sodium. On the other hand, the band at 1128 cm^{-1} can be attributed to Hypromellose. The band that is observed at 1064 cm^{-1} belongs to Hypromellose, one of the shoulders observed at the cluster of bands of the solid substance at the wavenumber range of 800-1174 cm^{-1}. In the same manner, the magnification of the region 1200-1550 cm^{-1} as depicted in the bottom of Figure III.41, reviled that the bands at 1228 cm^{-1}, 1420 cm^{-1}, 1460 cm^{-1} and 1482 cm^{-1} can be attributed to warfarin sodium. In the cluster of peaks at the region 1400-1500 cm^{-1}, a band at 1443 cm^{-1} is obvious in all films. However, none of the solid substances appear to have a band at that wavenumber. On the other hand, solid Hypromellose appears to have a band at 1456 cm^{-1}, which might be the one appearing in the films at 1443 cm^{-1}. Furthermore, the band at 1460 cm^{-1} attributed to warfarin sodium could also partially be attributed to Hypromellose as the solid substance has a band at 1458 cm^{-1}.



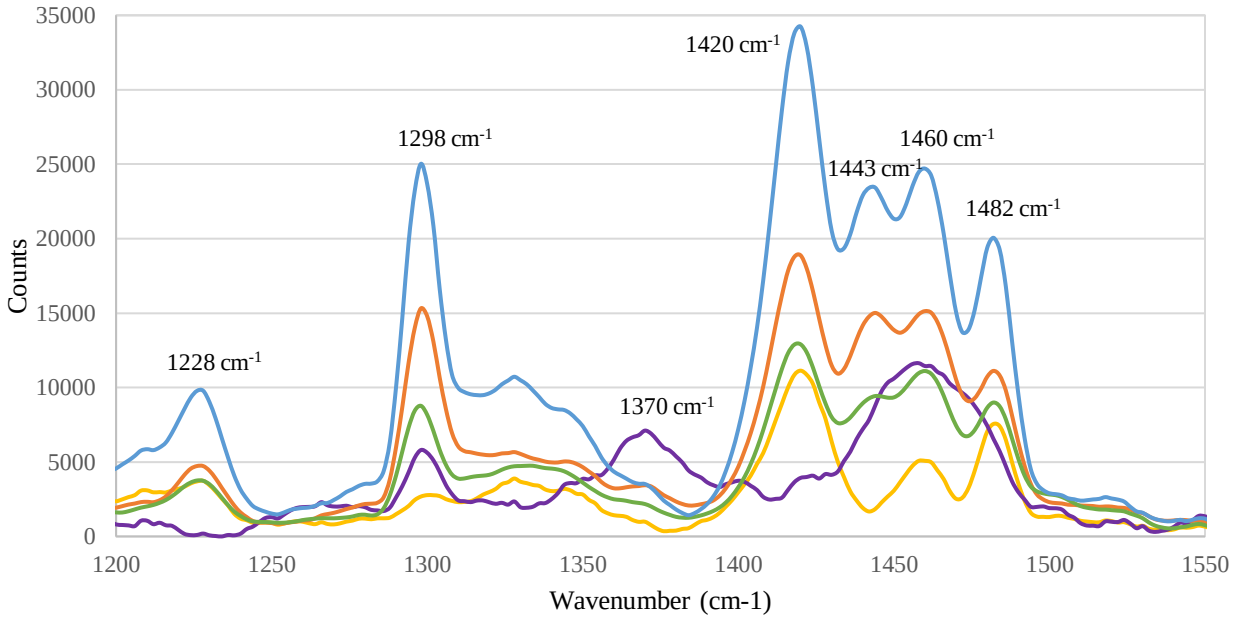


Figure III.41: Magnification of Raman spectra of dry films. Orange line: film from 2.5% gel, green line: film from 5% gel, blue line: film from 7.5% gel, yellow line: Warfarin sodium solid substance and purple line: Hypromellose solid. (Top) wavenumber range: 980-1200 cm^{-1} and (bottom) wavenumber range: 1200-1550 cm^{-1}.

Raman spectroscopy could be a useful tool for the identification of the constituents of the dry film. In all films tested, all bands could be attributed to either warfarin sodium or Hypromellose and the API could be identified in the samples with confidence more than 90%. Thus, Raman spectroscopy can be used as an in-process quality control method to ensure that the produced final product is of ensured quality. A drawback of the present method is that it could not be used as an in-process method for the %assay determination of the API. Unfortunately, as with the bulk gels, there was no consistency in the intensity of the signal. Several Raman spectrums were recorded in different areas of the film, and they were not in agreement, showing different intensity signals even at the same area. The same was observed with the films with different concentrations. As shown in Figure III.40, the intensity of the bands for the film with lower API amount, e.g. the film from 2.5% gel is higher than the film from 5% gel or the raw material. The same was also observed when dissolving the films and recording the Raman spectrum of the solutions. Thus, Raman spectroscopy can be a quality control for the identification of the API in the final product but not for the %assay determination (Table III.21).

Table III.21: Identification and %Assay results of Warfarin sodium in dry films with Raman spectrometry.

Identification of Warfarin Sodium with Raman at 1608 cm^{-1}	**%Assay determination of Warfarin Sodium with Raman at 1608 cm^{-1}**
√	X
√	X
√	X

Information Flow

Since the built system is a "*Pharma 4.0*" tool that is able to produce customized pharmaceutical products according to the patients' needs, apart from the quality controls during the production, it is of great

importance the information acquired at each process step that it is stored, tracked and available. This is possible by connecting all the relevant equipment in a centralized database as depicted in Figure III.18.

In accordance with the principles of Quality by Design, once the Quality Target Product Profile (QTPP) has been set, the Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) are set and stored under a unique code. This code generated is characterized by the patient, the delivery system parameters, the batch size, the process parameters, the controls that are going to be performed, the personnel and all the relevant to the patient, product, and process information. All these characteristics synthesize the "*Master Manufacturing Formula"* which is stored in an on-line database and is available to the physician. In the present case study, the Master Manufacturing Formula includes the API selection, Warfarin Sodium, the customized dose, the pharmaceutical form, which is the orodispersible film, the raw materials, which consist of the API, Hypromellose and water, the shape and size of film according to the dose as well as the number of films to be print according to the prescription. Furthermore, all the process parameters such as the type of syringe and needle, printing speed, layer height and count are included in the Master Manufacturing Formula. All the quality controls to be performed with the reference prototypes such as UV/Vis, FT-IR or Raman spectrums are stored in the database along with data to support the Machine Vision control.

During the production process, all the relevant information from each process step, such as dose, identification, %assay or shape check, are recorded and stored to the respective section in the database under the unique code of the *Master Manufacturing Formula*. In this way, all the information from the specific production process and product are stored and tracked. Regardless of the production outcome, the authorized personnel are able to follow the whole process based on scientific data. For example, in the case of the orodispersible films, if the wrong API is used by accident, the identification control of the raw materials or worst-case scenario after printing, will reject the production based on the IR spectra that are recorded and compared to the references available in the database. Also, if the process fails to complete the production of the film correctly and non-conforming films are produced, Machine Vision will reject the film and the defected product will never reach the patient. All the information and the data supporting the approval or rejection of the produced batch are recorded and stored within the Master Manufacturing Formula.

This whole system is not a one-way process, as the interaction between the different equipment and controls gives feedforward and feedback information, providing the capability of machine learning through detection of faults and failures, thus train the system in order to result in more accurate outcomes. Through artificial intelligence, the system could potentially be able to schedule production or predictive maintenance based on the information collected from the different sources. Last but not least, through remote access, the authorized personnel would be able to remotely access the system and monitor the equipment parameters and the whole production process.

In conclusion, the information flow internally and externally to the system provides all the information needed for the compounding of drug products at the point of need. Based on scientific data in combination of smart manufacturing, quality assurance in real time of both the critical quality characteristics of the final product and the critical parameters of the production process, is possible assuring that no defected products will end up to the patient.

IV. CONCLUSIONS

This chapter will conclude the study by summarizing the key research findings in relation to the research aims and discussing the value and contribution thereof. The overall conclusions of the study are the following:

- This research work demonstrates the applicability of 3D printing in preparing personalized dosage forms according to the personalized individual needs of each different patient at the point of need.
- 3D printing can be employed at the point of need in order to prepare small batches of dosage forms according to the principal of "on-demand manufacturing".
- Special product characteristics such as tailored release profiles, accurate dose or complex designs can be achieved with the implementation of 3D printing.
- 3D printing technology is able to easily tune the final dosage form prepared by simply modifying the design characteristics through changes in the software and CAD.
- 3D printing is an accurate and reproducible method, cost effective and environmentally friendly that is in line with the modern production approaches such as Lean and Agile Manufacturing. It is a fast, reproducible, and single-step method that produces the dosage form with the desired quality attributes quickly and easily without losses and waiting times between different process steps, as in Lean manufacturing. The flexibility of the "Agile manufacturing" approach is achieved, as simple modifications in the CAD file can produce multiple versions of the same product with various quality attributes to meet personalized requirements of each user.
- 3D printing in combination with Design of Experiments, a major tool for the implementation of statistical thinking and Quality by Design in pharmaceutical development, is a simple and reliable methos for fine-tuning critical quality attributes, such as customized release profiles and dose.
- 3D printing technology can be applicable in dosage forms prepared with conventional manufacturing processes in order to modulate the drug release rate according to the patient needs, without altering the core composition/manufacturing method of the formulation.
- For both the hydrophilic and lipophilic APIs, different dissolution profiles can be achieved by simply tuning three coating parameters controlled by the 3D printer, namely the surface coverage, number of the applied layers and the number of the coating sides.
- The development of a system that implements Pharma 4.0 key enabling technologies such as 3D printing and Machine Vision combined with analytical methodologies such as UV/Vis spectrophotometry, FT-IR or Raman spectroscopy, is able to adequately manage the risks associated with the medication errors. The risks of delivering the wrong API and dose in a clinical setting can be mitigated through this Process Wide Quality Control system that has been developed and assured both quality and traceability during the whole production process.
- The system's approach presented could be the basis for the production of small batches and fully customized dosage forms without the need of complex equipment and processes, at the point of

need, complying with the quality guidelines and mitigating the patient risks associated with compounding activities performed in Community and/or Hospital Pharmacies.

- The system designed is patient centered and flexible, a solution that can be easily implemented in a Community and/or Hospital Pharmacy.
- In line with the modern regulatory directives and the smart manufacturing approach, the entire supply chain of a personalized drug product, from the raw materials and through its manufacturing process to the patient, is recorded and fully traceable in order to ensure product quality and patient safety through systems thinking and acting.
- This research work demonstrates that 3D printing can be a new technology employed in the pharmaceutical sector in order to produce new pharmaceutical forms with customized release profiles, various designs, and doses according to the individual needs of the patient. It is in line with all the modern quality guidelines as it incorporates Quality by Design and Quality Risk Management and ensuring product quality.
- This work offers an improved approach for the compounding activities performed in everyday practices for the production of personalized medicinal products. In contrast to the established techniques followed, the developed approach achieved not only the production of customized dosage forms but also ensured both quality and traceability during the whole production process. Through this system is now possible to identify and minimize the possibility of error during the compounding activities, before administering the product to the patient.

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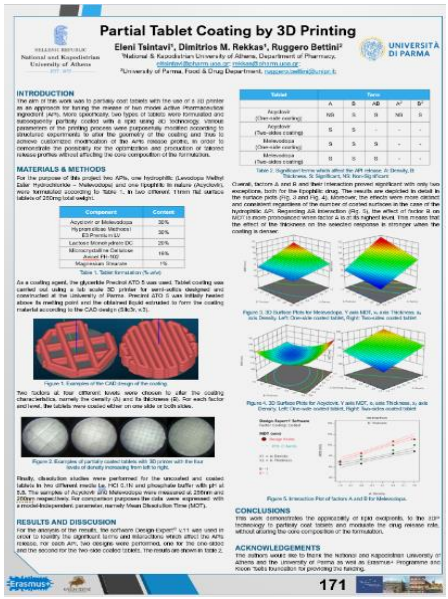

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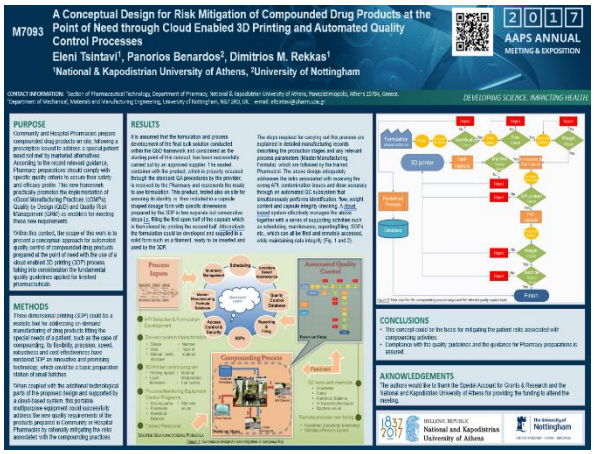

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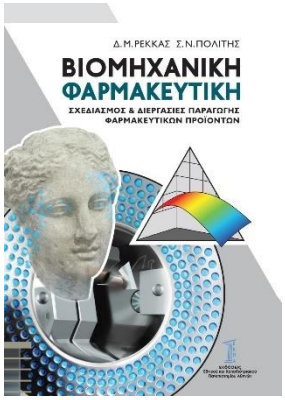

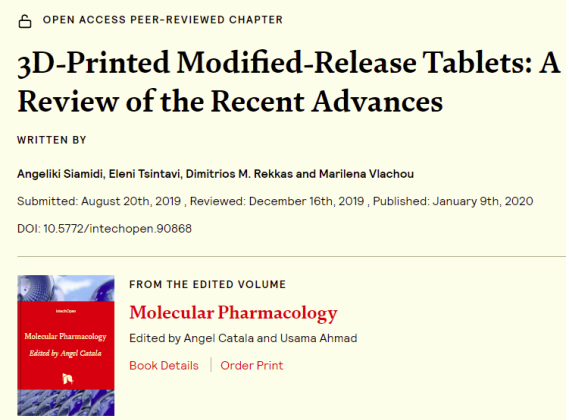
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3D-Printed Modified-Release Tablets: A Review of the Recent Advances

WRITTEN BY

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APPENDIX

Chapter I.1: 3D Printing & Industry 4.0

Figure A.1: GoogLeNet (Szegedy et al., 2014).

Chapter II: Materials & Methods

Table A.1: 3D Printing parameters as set to software Slic3r (v.3)

Printer settings	Filament settings	Print settings
1. Size and coordinates: • Bed shape: Circular 11.28 mm diameter • Z offset: 0 mm	1. Filament: • Colour: white • Diameter: 8.66 mm • Extrusion multiplier: 1 • Temperature: Extruder first layer: 60 oC Extruder other layers: 60 oC Bed first layer: 50 oC Bed other layers: 50 oC	1. Layers and perimeters: • Layer height: 0.3 mm • First layer height: 0.3 mm • Perimeters: 0
2. Capabilities: • Extruders: 1 • With heated bed	2. Cooling • Fan speed: 100%	2. Infill: • Fill density: 25%, 50%, 75% or 100% • Fill pattern: Rectilinear • Combine infill every: 1 layer • Fill gaps: enabled • Solid infill every: 0 layers (disabled) • Fill angle: 0o • Solid infill threshold area: 70 mm^2
3. Firmware: • RepRap (Marlin/Sprinter)		3. Skirt and Brim: • Disabled
4. Custom G-code • Start and End G-code		4. Support material: • Disabled
5. Extruder settings • Nozzle diameter: 0.45 mm • Limits: min: 0.15 mm, max: 0.3 mm • Offset: x:0, y:0 mm • Retraction: disabled		5. Speed: • Perimeters: disabled • Infill: 2.1 mm/s sold, top solid, gaps : disabled • Bridges: 6 mm/s • Support material: disabled • Speed for non-print moves: Travel 130 mm/s • Modifiers: First layer speed: 100% • Acceleration control: disabled • Autospeed: disabled

6. Multiple extruders:
   - Infill extruder: 1
   - Ooze prevention: disabled
   - Regions/extruders overlap: 0 mm

7. Advanced:
   - Extrusion width:
     Default extrusion width: auto
     First layer: default
     Infill: default
   - Overlap:
   - Infill/perimeters overlap: 15%
   - Flow:
   - Bridge flow ratio: 1
   - Other:
   - XY Size compensation: 0 mm
   - Resolution (deprecated): 0 mm

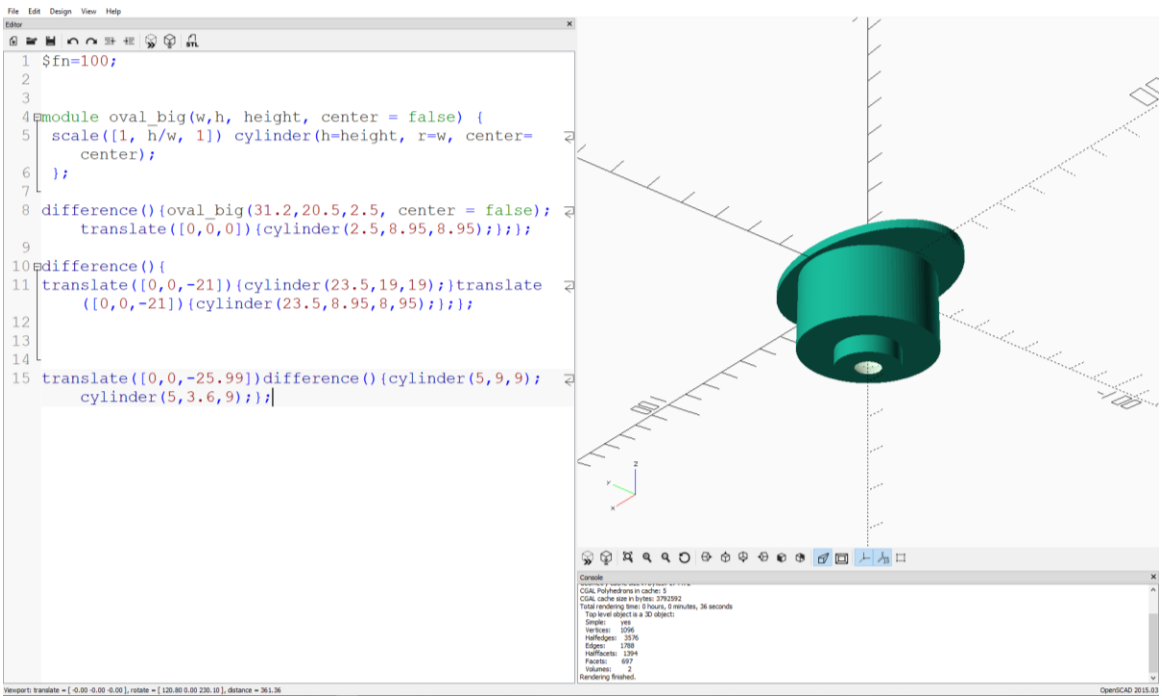
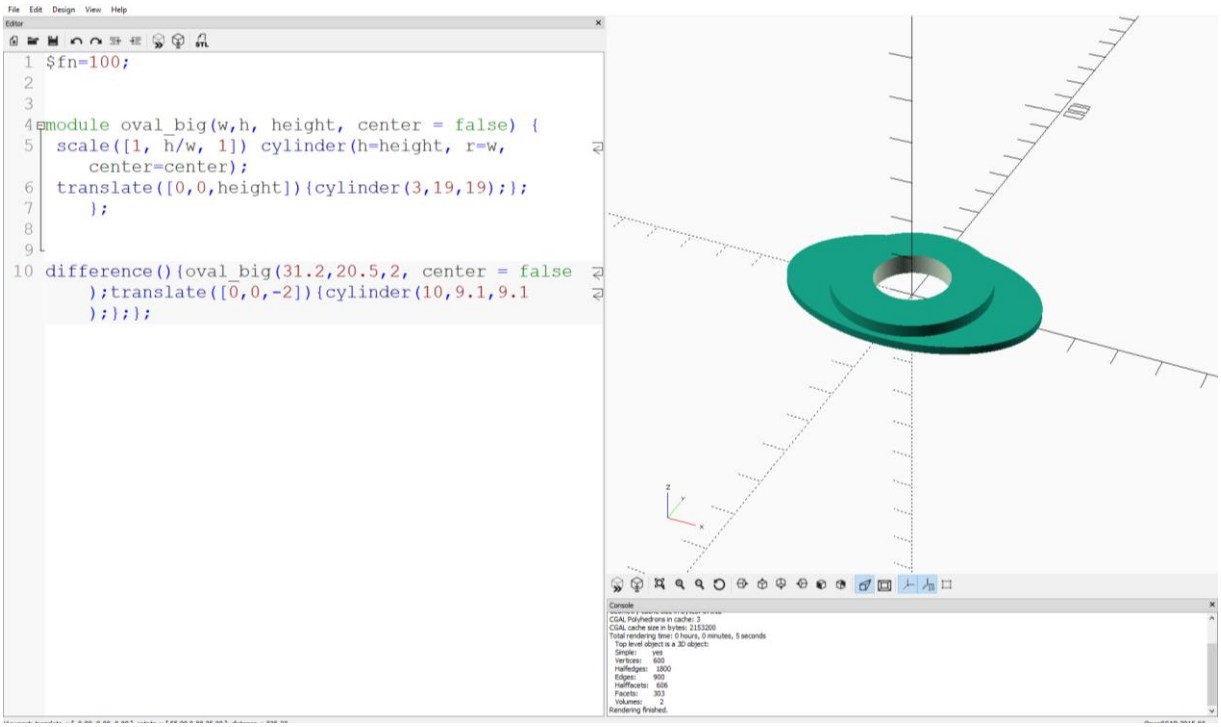


Figure A.2: OpenSCAD file for bottom support 10.0 ml syringe adaptor.

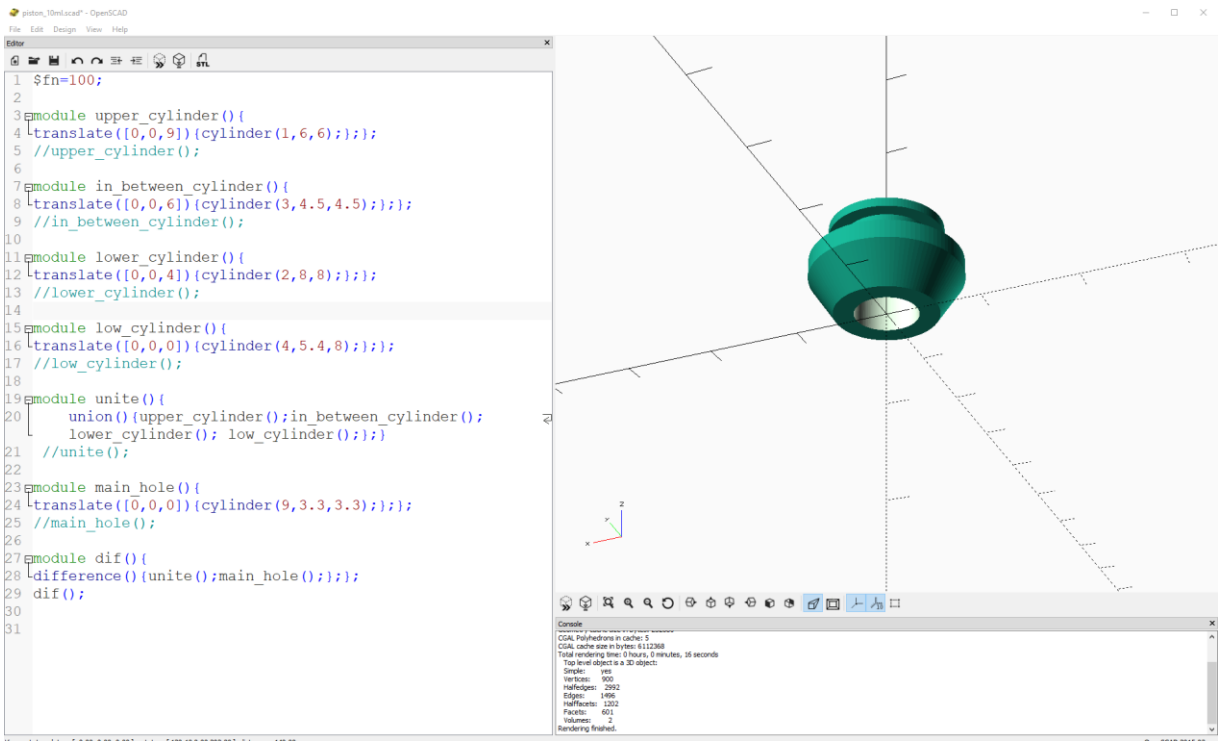


```
$fn=100;


module oval_big(w,h, height, center = false) {
 scale([1, h/w, 1]) cylinder(h=height, r=w,
    center=center);
 translate([0,0,height]){cylinder(3,19,19);};
    };


difference(){oval_big(31.2,20.5,2, center = false
    );translate([0,0,-2]){cylinder(10,9.1,9.1
    );};};};
```

Figure A.3: OpenSCAD file for top support 10.0 ml syringe adaptor.



```
$fn=100;

module upper_cylinder(){
translate([0,0,9]){cylinder(1,6,6);};};
//upper_cylinder();

module in_between_cylinder(){
translate([0,0,6]){cylinder(3,4.5,4.5);};};
//in_between_cylinder();

module lower_cylinder(){
translate([0,0,4]){cylinder(2,8,8);};};
//lower_cylinder();

module low_cylinder(){
translate([0,0,0]){cylinder(4,5.4,8);};};
//low_cylinder();

module unite(){
    union(){upper_cylinder();in_between_cylinder();
    lower_cylinder(); low_cylinder();};}
 //unite();

module main_hole(){
translate([0,0,0]){cylinder(9,3.3,3.3);};};
//main_hole();

module dif(){
difference(){unite();main_hole();};};
dif();
```

Figure A.4: OpenSCAD file for piston of 10.0 ml syringe adaptor.

Table A.2: Printing parameters for 10.0 ml syringe adaptors as set to software Voxelizer v.1.4.18.

General settings	Outline	Infill	Project
Print-head: FDM Dual PRO	Outline count: 2	Infill print speed: 40mm/s	Bottom layer base: empty
Filament: PLA 1.75mm	Outline print speed: 50mm/s	Infill ratio: 100%	Filament diameter: 1.75mm
Nozzle temperature: 210ºC	Simplification threshold: 0.02mm	Infill offset: -0.05mm	Bottom layer extrude: extruder 1
Bed temperature: 65ºC	Minimum outline length: 1mm	Infill angle: 0 eg	Home before printing: YES
Extruder 1	Outline order: inward	Infill type: rectilinear	Add custom gcode: NO
Fan speed: 60%	Border inset: 0mm	Top solid depth: 1mm	Head change artifact: brim
Fan free layers: 3	Start position: complex	Bottom solid depth: 1mm	Extruder 1 print speed: 100%
Infill ratio: 100%	Small perimeter speed: 15mm/s	Solid depth: 0.5mm	Extruder type: unified head
Infill type: rectilinear	Small perimeter threshold: 10mm	Solid bottom layers: 3	Visibility: ambient occlusion
Bottom layer base: empty			Support: NO
Layer height: 0.3mm			
First layer height: 0.2mm			
Path width: 0.4mm			
Travel speed: 80mm/s			
First layer speed: 100%			
Retraction: ON			
Retraction height: 0.1mm			
Retraction amount: 4.5mm			
Retraction speed z: 50mm/s			
Retraction speed e: 30mm/s			
Retraction min distance: 10mm			
Extra length on restart: 0mm			
Travel extension multiplier: 3			
Generators order: outline -> infill			

Table A.3: Printing parameters of Orodispersible Film as set to software Voxelizer v.1.4.18

General settings	2D extrusion setting	Material dimensions
Print-head: Chocolate\Ceramics	Filament diameter: 5mm	Material height: 2mm
Syringe: 10.0 ml	Layer count: 2	Centre x: 117.5mm
Nozzle temperature: Ambient	Layer height: 0.1mm	Centre y: 125mm
Bed temperature: Ambient	Path width: 3mm	Width: 200mm
Needle: G26	Travel speed: 120mm/s	Depth: 100mm
	Print speed: 12mm/s	
	Extrusion order: Proximity	
	Retraction: OFF	

Chapter III: Results & Discussion

III.1. Partial Tablet Coating by 3D Printing

Drug Release Profiles of Melevodopa coated tablets

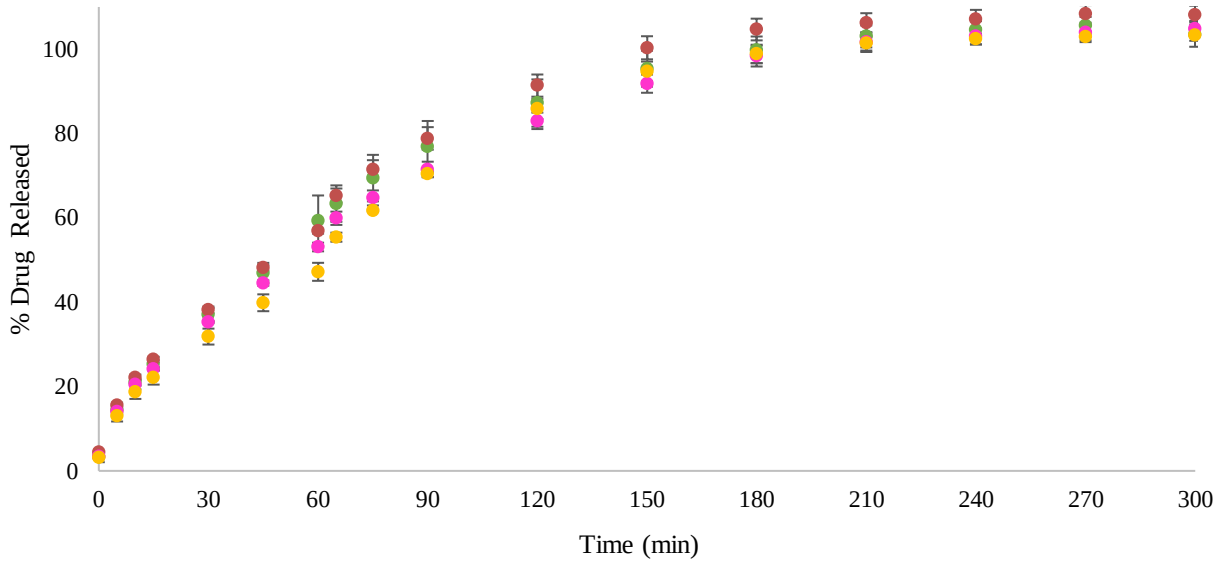


Figure A.5: Melevodopa release profiles of one side coated tablets; mean value ± SD (n = 3). Factor A is constant at 25%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

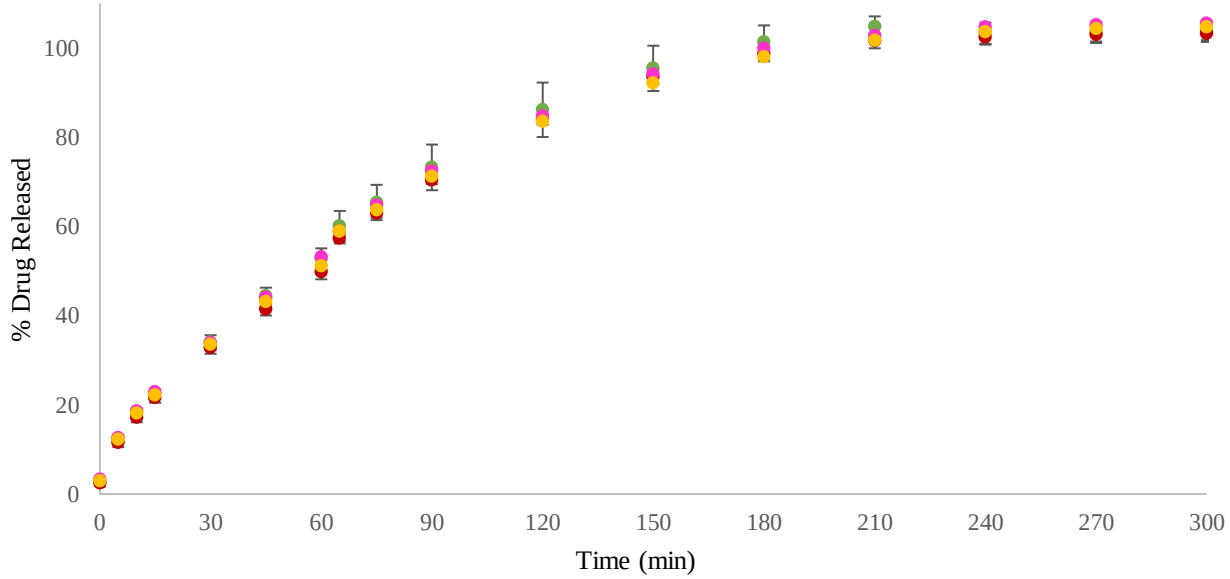


Figure A.6: Melevodopa release profiles of two side coated tablets; mean value ± SD (n = 3). Factor A is constant at 25%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

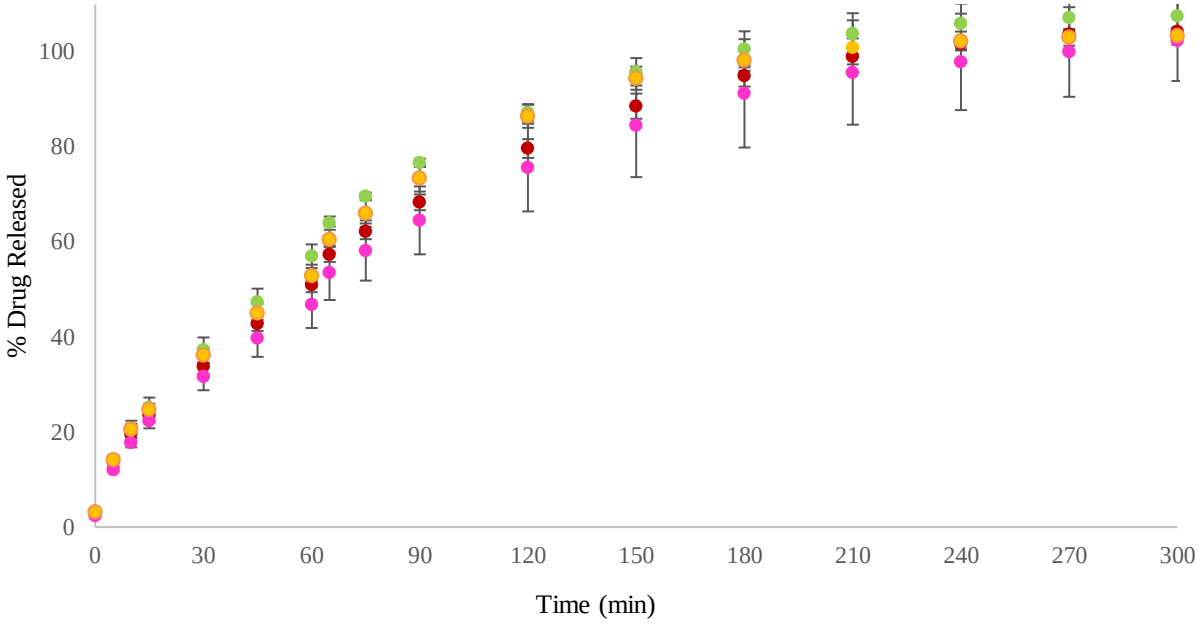


Figure A.7: Melevodopa release profiles of one side coated tablets; mean value ± SD (n = 3). Factor A is constant at 50%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

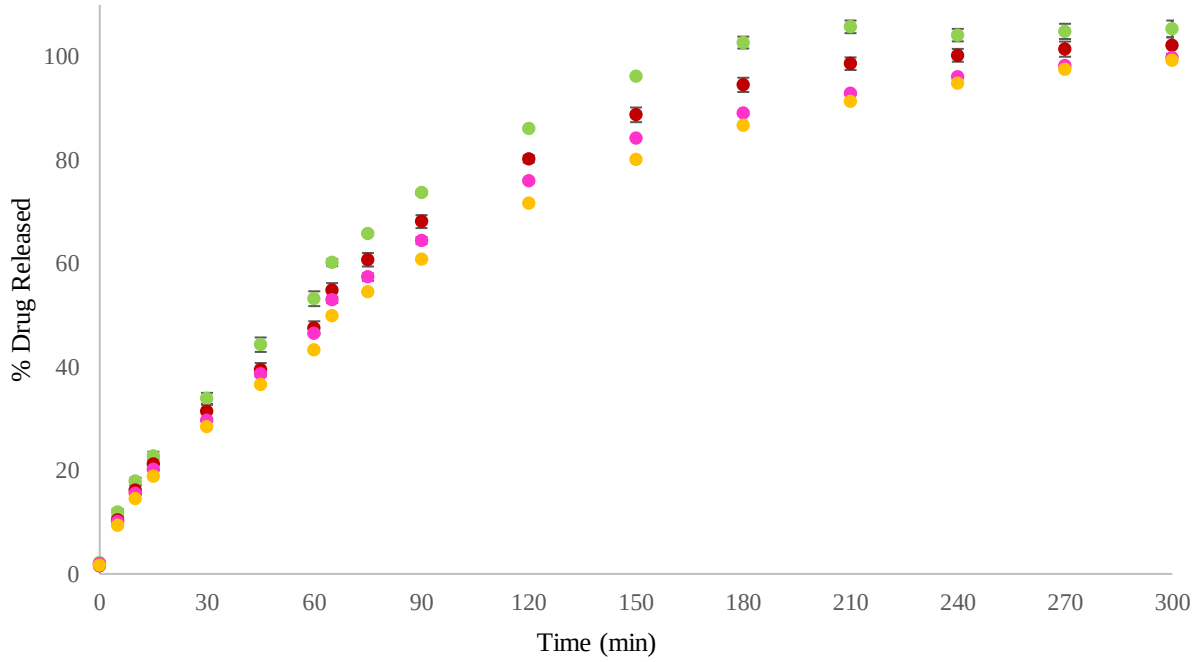


Figure A.8: Melevodopa release profiles of two sides coated tablets; mean value ± SD (n = 3). Factor A is constant at 50%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

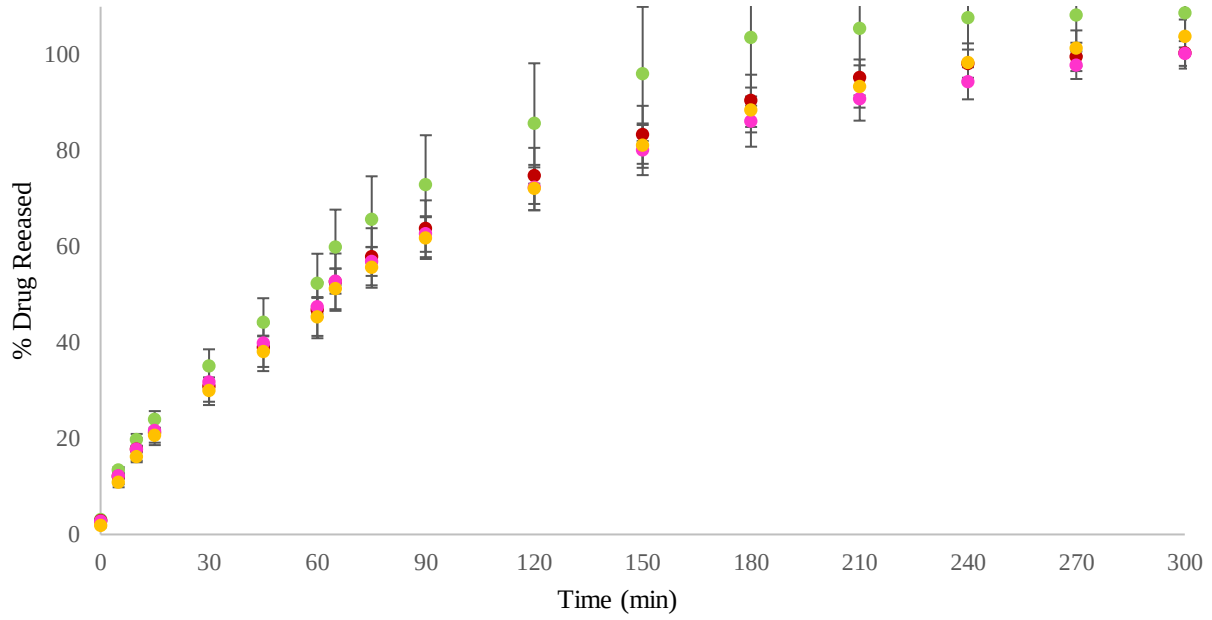


Figure A.9: Melevodopa release profiles of one side coated tablets; mean value ± SD (n = 3). Factor A is constant at 75%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

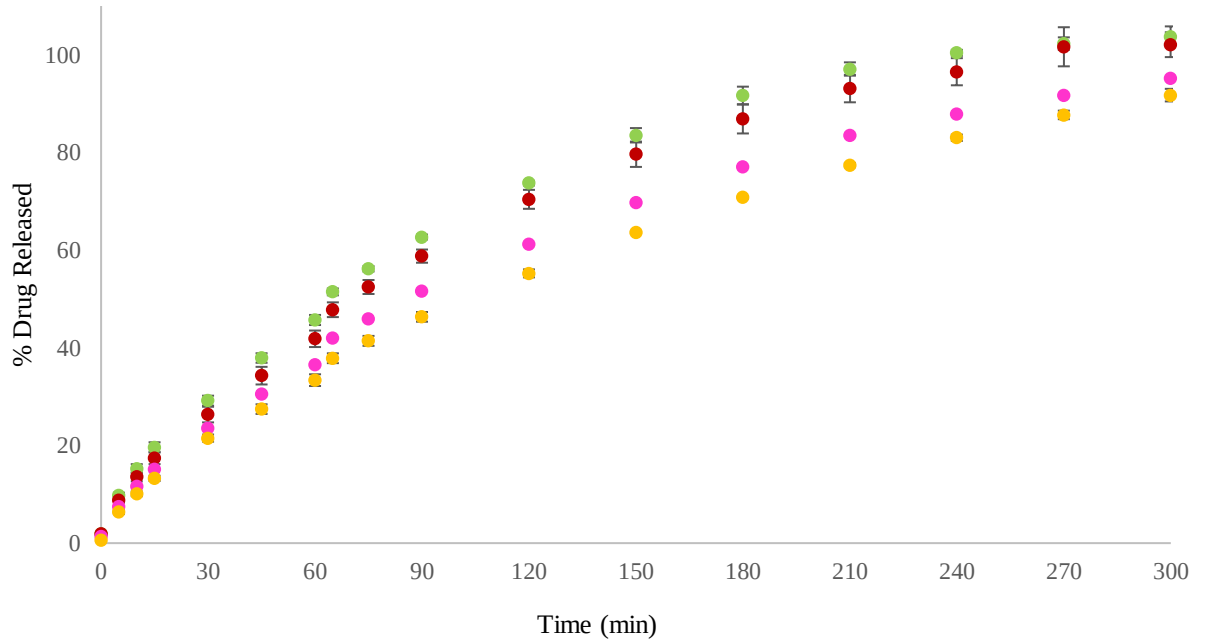


Figure A.10: Melevodopa release profiles of two sides coated tablets; mean value ± SD (n = 3). Factor A is constant at 75%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

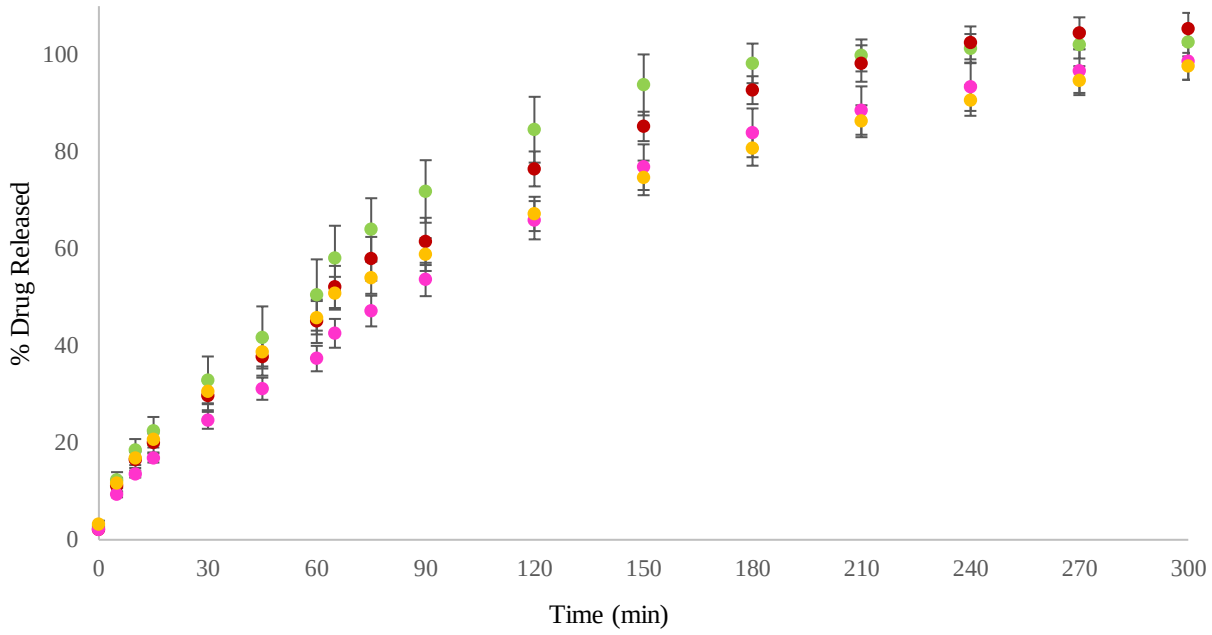


Figure A.11: Melevodopa release profiles of one side coated tablets; mean value ± SD (n = 3). Factor A is constant at 100%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

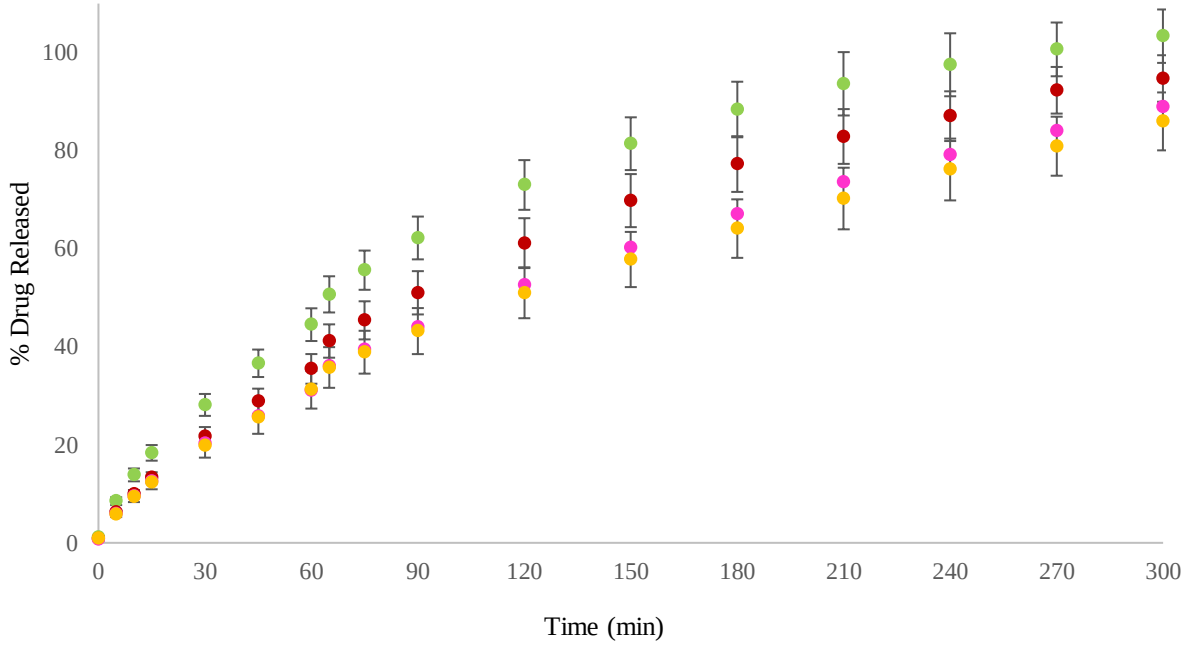


Figure A.12: Melevodopa release profiles of two sides coated tablets; mean value ± SD (n = 3). Factor A is constant at 100%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

Drug Release Profiles of Acyclovir coated tablets

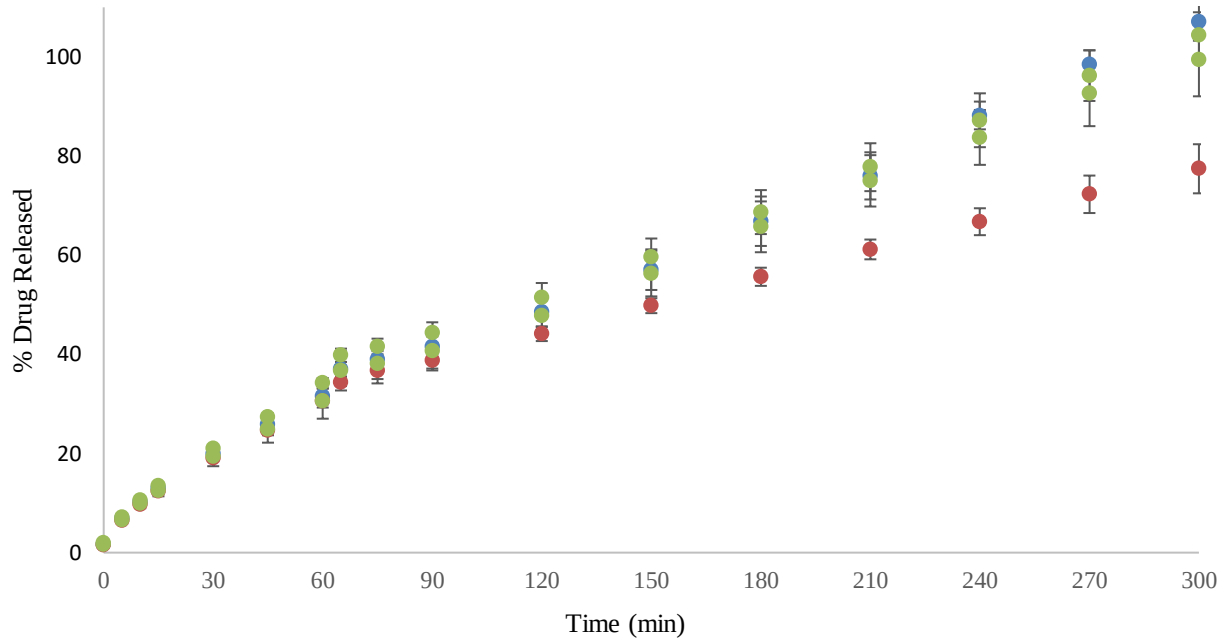


Figure A.13: Acyclovir release profiles of one side coated tablets; mean value ± SD (n = 3). Factor A is constant at 25%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

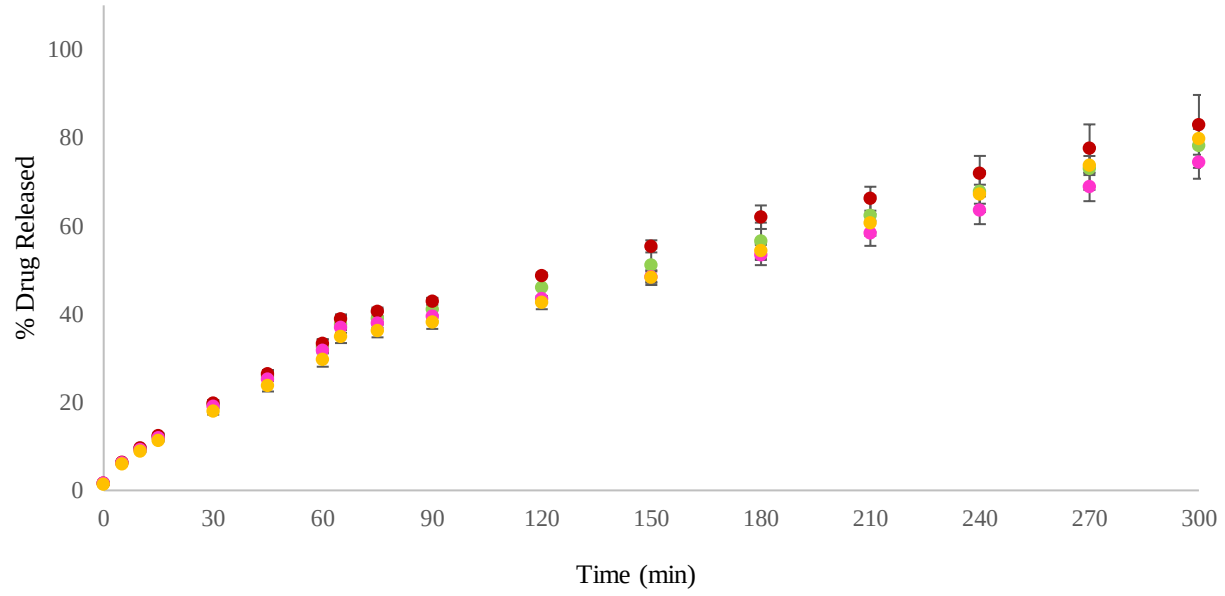


Figure A.14: Acyclovir release profiles of two sides coated tablets; mean value ± SD (n = 3). Factor A is constant at 25%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

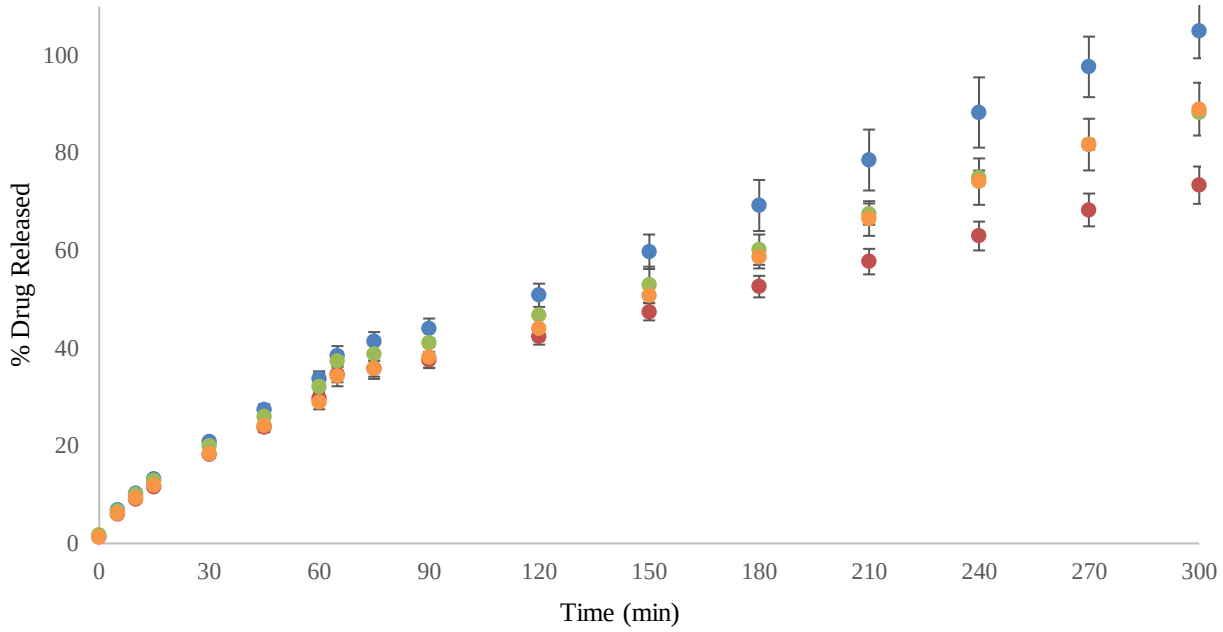


Figure A.15: Acyclovir release profiles of one side coated tablets; mean value ± SD (n = 3). Factor A is constant at 50%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

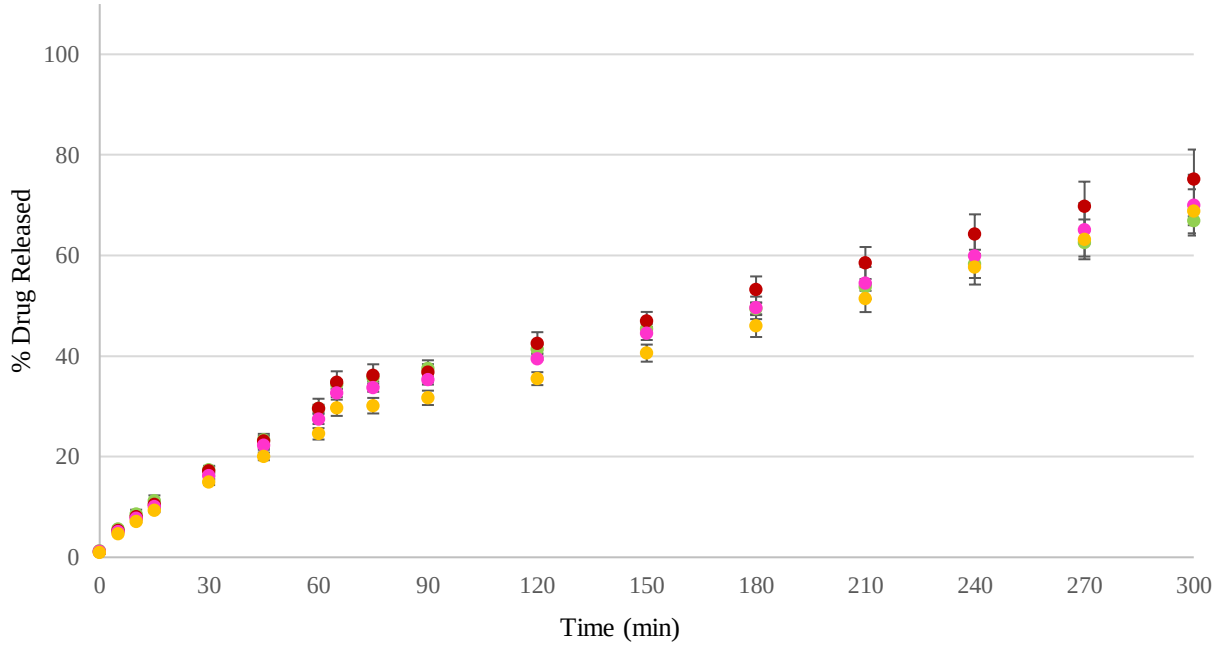


Figure A.16: Acyclovir release profiles of two sides coated tablets; mean value ± SD (n = 3). Factor A is constant at 50%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

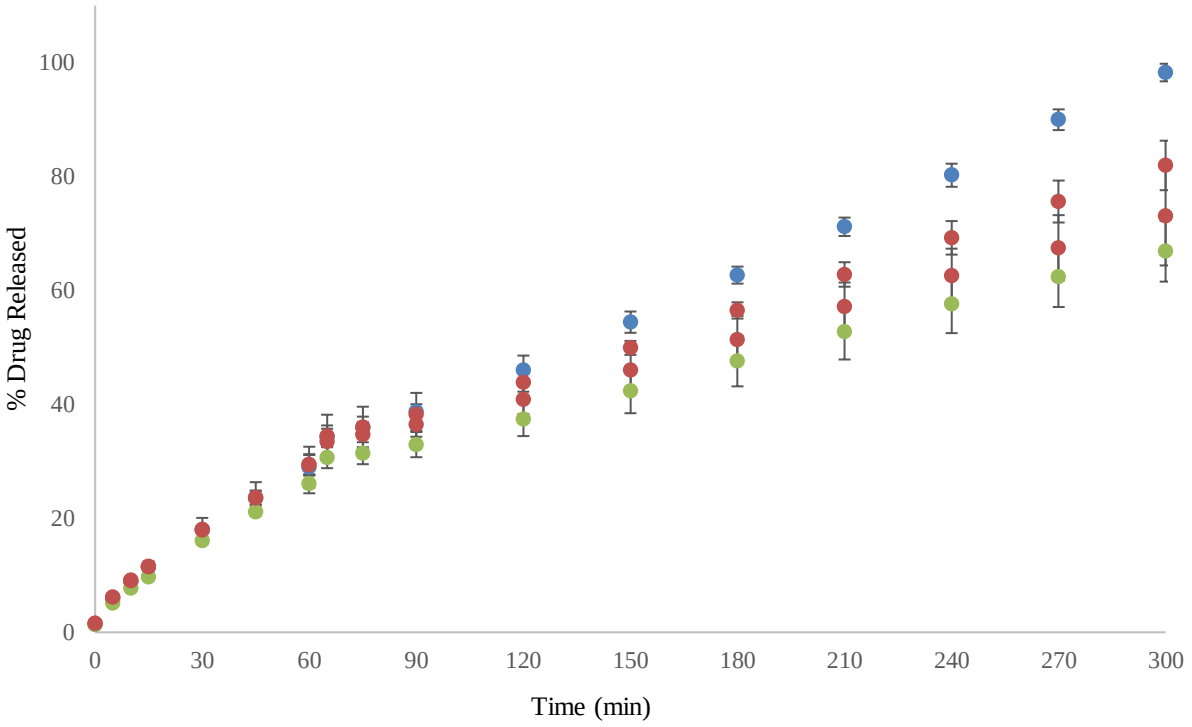


Figure A.17: Acyclovir release profiles of one side coated tablets; mean value ± SD (n = 3). Factor A is constant at 75%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

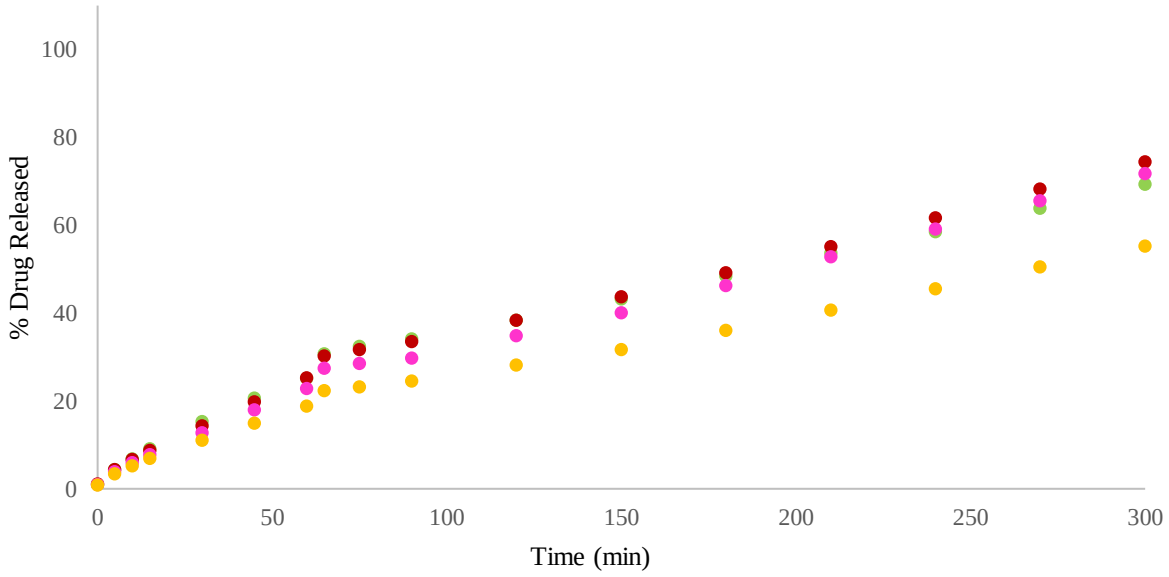


Figure A.18: Acyclovir release profiles of two sides coated tablets; mean value ± SD (n = 3). Factor A is constant at 75%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

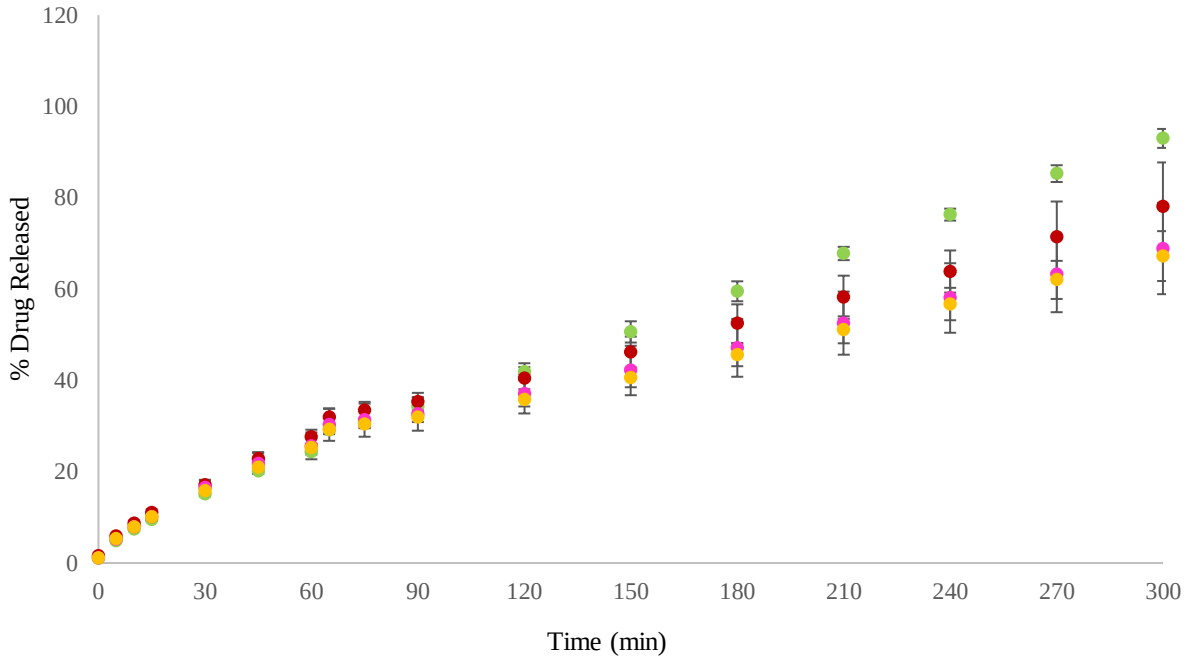


Figure A.19: Acyclovir release profiles of one side coated tablets; mean value ± SD (n = 3). Factor A is constant at 100%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

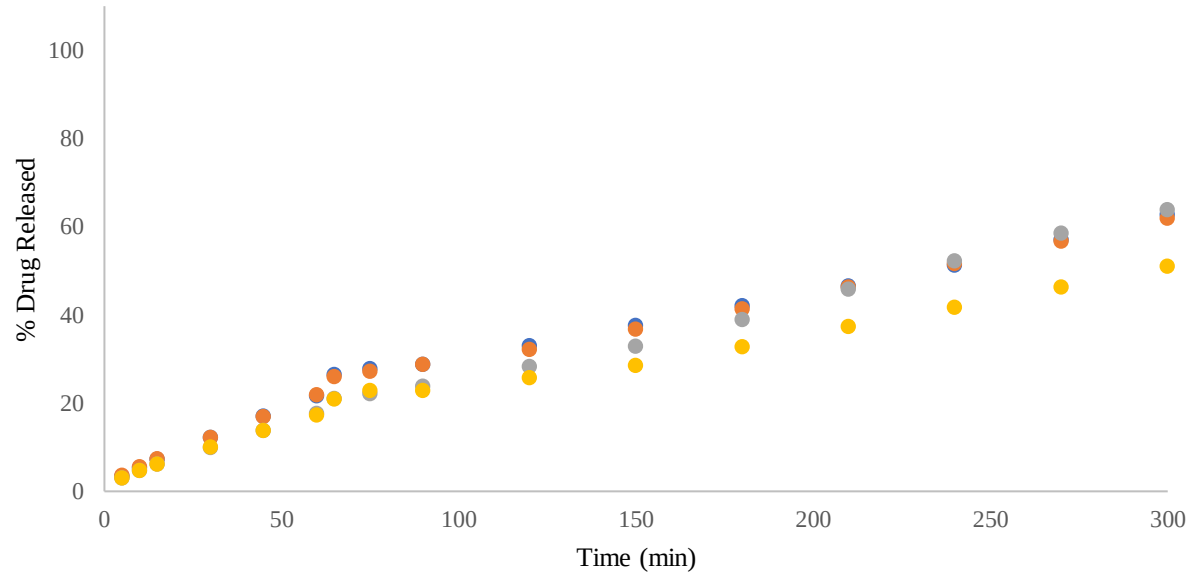


Figure A.20: Acyclovir release profiles of two sides coated tablets; mean value ± SD (n = 3). Factor A is constant at 100%, while factor B varies from 2 to 8 layers. Green circle: factor B 2 layers, red circle: factor B 4 layers, pink circle: factor B 6 layers and yellow circle: factor B 8 layers.

III.2. A 3D Printing and Machine Vision Application for Quality Risk Management in Compounding Drug Products at the Point of Need

UV/Vis Spectrophotometry

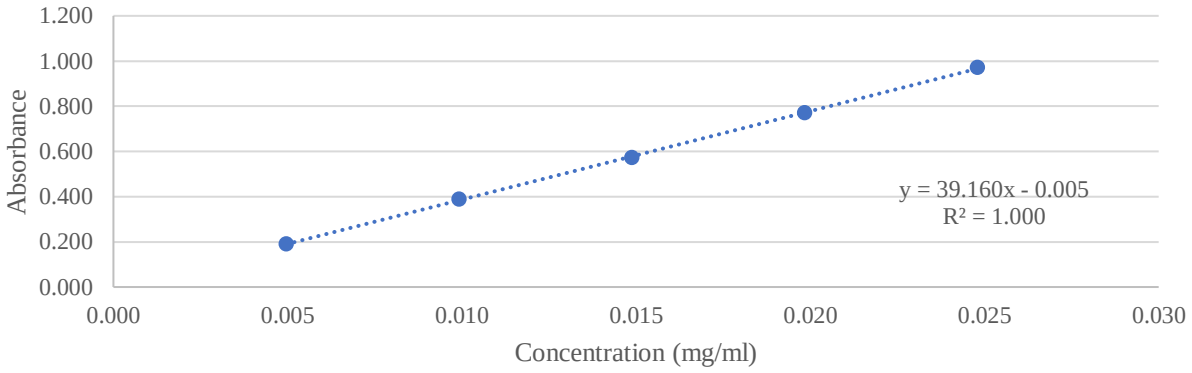


Figure A.21: Example of calibration curve of UV/Vis during the quantification of Warfarin sodium in gels or films; mean value ± SD (n = 3).

Table A.4: ANOVA table of calibration curve of UV/Vis during the quantification of Warfarin sodium in gels or films.

	df	SS	MS	F	Significance F	
Regression	1	0.3786916	0.3786916	14490.75	1.26394E-06	
Residual	3	7.84E-05	2.61333E-05			
Total	4	0.37877				
	Coefficients	**Standard Error**	**t Stat**	**P-value**	**Lower 95%**	**Upper 95%**
Intercept	-0.0058	0.005361592	-1.081768291	0.358553714	-0.022862978	0.011262978
X variable 1	39.23387097	0.325923539	120.3775311	1.26394E-06	38.19663681	40.27110513

IR Spectroscopy

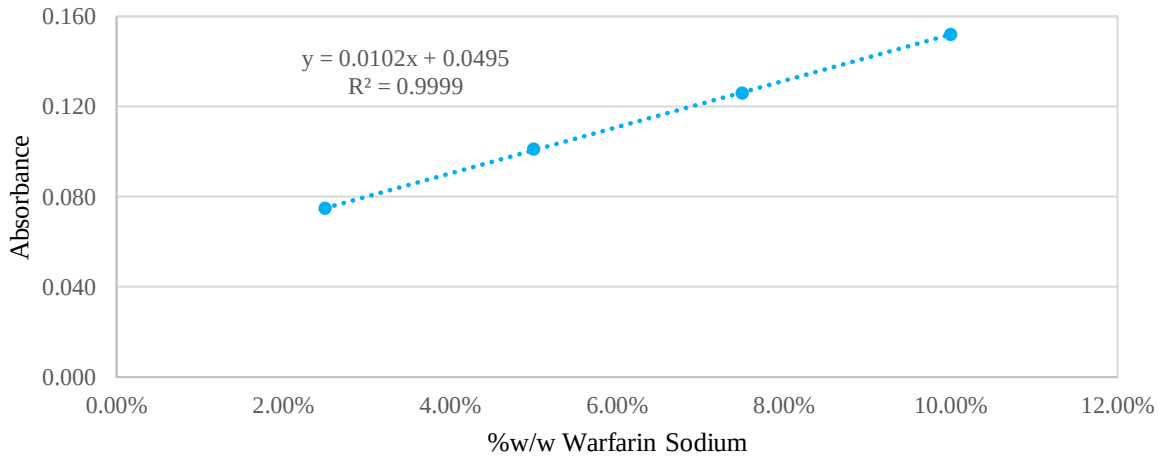


Figure A.22: Calibration Curve for IR absorbance of Warfarin Sodium

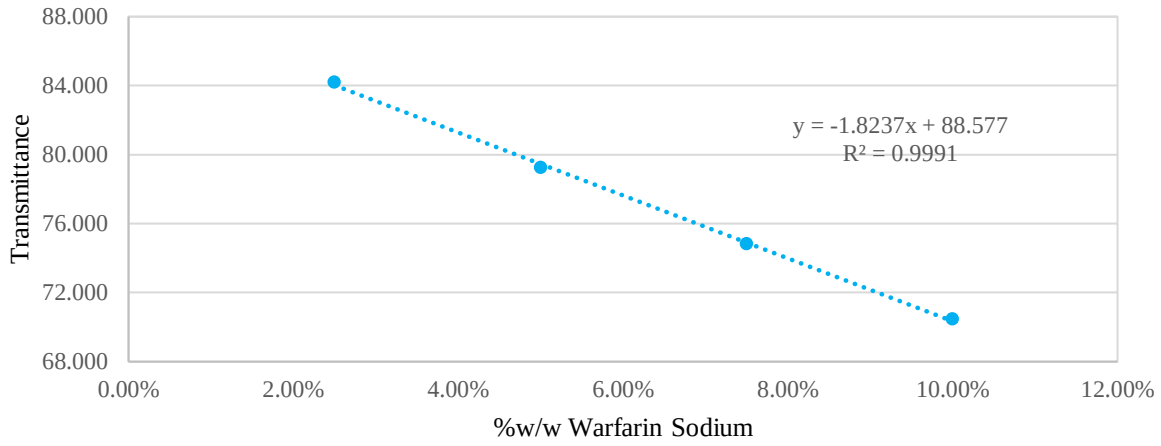


Figure A.23: Calibration Curve for IR transmittance of Warfarin Sodium

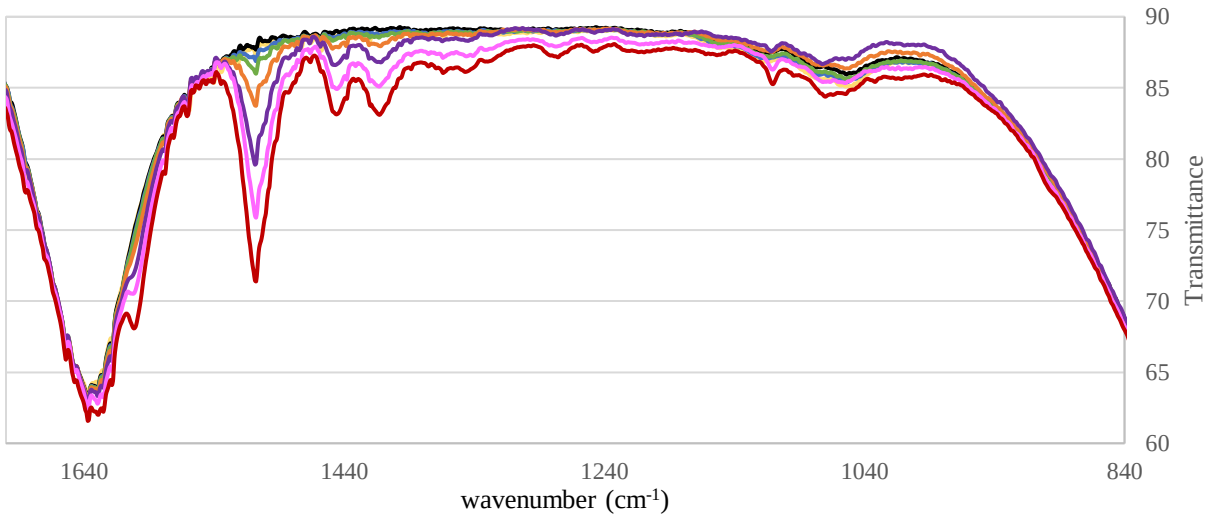


Figure A.24: IR spectrum of Warfarin Sodium gels in various concentrations (%w/w). Yellow line: placebo gel, black line: 0.1%, blue line: 0.5%, green line: 1.0%, Orange line: film from 2.5%, purple line: 5.0%, pink line: 7.5% and red line: 10%.

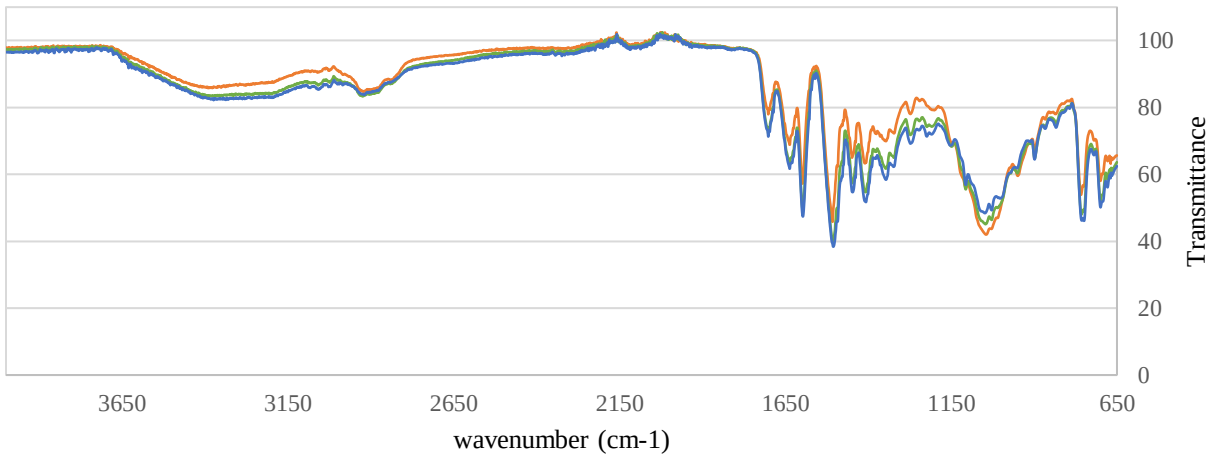


Figure A.25: IR spectrum of 15 mm Warfarin Sodium orodispersible films. Orange line: film from 2.5% Warfarin sodium gel, green line: film from 5.0% Warfarin sodium gel and blue line: film from 7.5% Warfarin sodium gel.

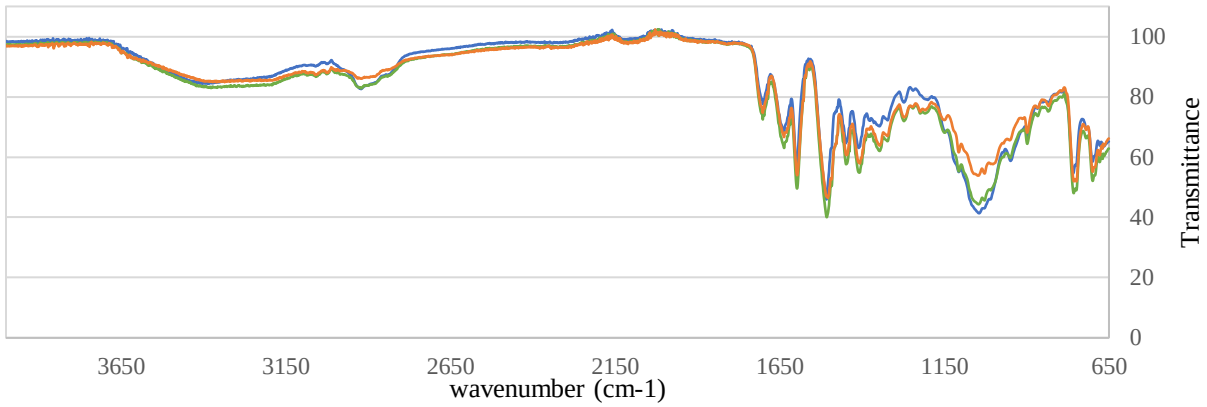


Figure A.26: IR spectrum of 25 mm Warfarin Sodium orodispersible films. Orange line: film from 2.5% Warfarin sodium gel, green line: film from 5.0% Warfarin sodium gel and blue line: film from 7.5% Warfarin sodium gel.

Raman spectroscopy

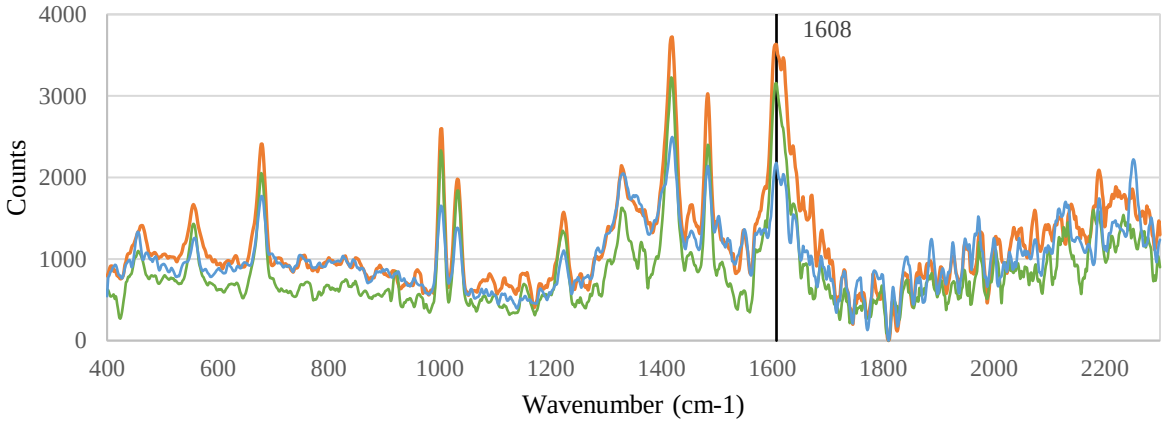


Figure A.27: Raman spectrum of Warfarin Sodium bulk gels (%w/w). Orange line: 2.5%, green line: 5.0% and blue line: 7.5%.

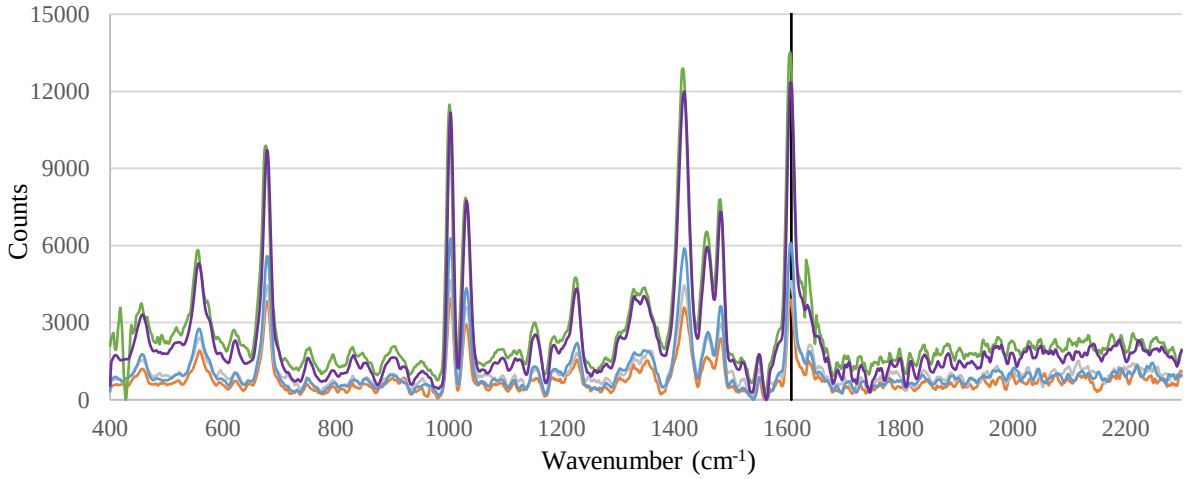


Figure A.28: Raman spectrum of films from Warfarin Sodium 2.5% w/w bulk gel. Orange line: measurement in the center of the film, green line: measurement in the corner of the film, blue line: measurement in the corner of the film, purple line: measurement in the corner of the film and grey line: measurement in the corner of the film.

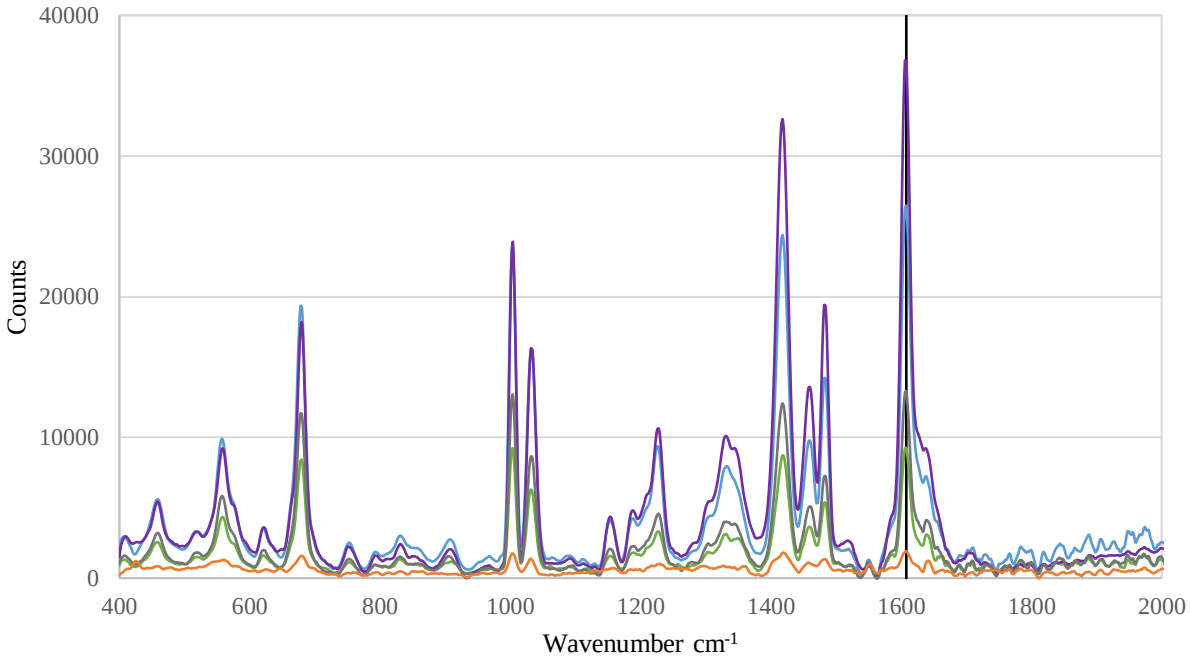


Figure A.29: Raman spectrum of films from Warfarin Sodium 5.0% w/w bulk gel. Orange line: measurement in the center of the film, green line: measurement in the corner of the film, blue line: measurement in the corner of the film, purple line: measurement in the corner of the film and grey line: measurement in the corner of the film.

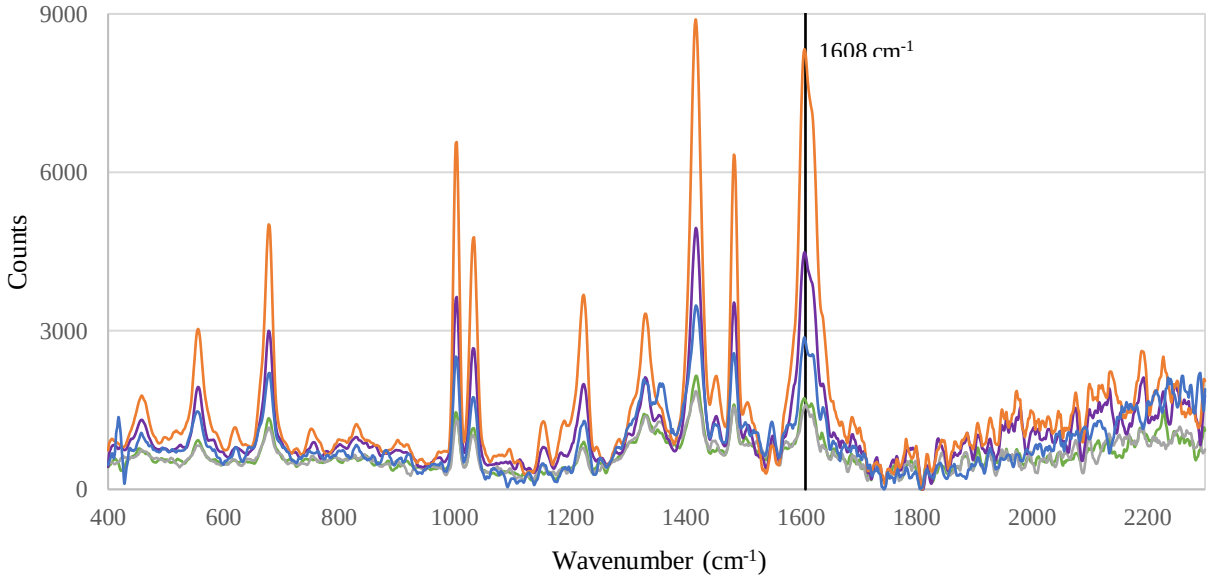


Figure A.30: Raman spectrum of films from Warfarin Sodium 7.5% w/w bulk gel. Orange line: measurement in the center of the film, green line: measurement in the corner of the film, blue line: measurement in the corner of the film, purple line: measurement in the corner of the film and grey line: measurement in the corner of the film.