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Drug disposition and characteristics of contents in the upper gastrointestinal lumen of healthy adults after a standard high-calorie high fat meal – Implications for the *in vitro* drug testing conditions

Doctoral Thesis

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Athens, 2020

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Περίληψη

Στόχοι

Να ποσοτικοποιηθεί η παρουσία στον ανώτερο γαστρεντερικό αυλό και να κατανοηθεί η διαδικασία της γαστρεντερικής μεταφοράς φαρμάκων με υψηλή εντερική διαπερατότητα, σε συνθήκες που προσομοιώνουν την κατάσταση μετά την αποσάθρωση φαρμακευτικών προϊόντων άμεσης αποδέσμευσης, στις μελέτες βιοδιαθεσιμότητας/βιοϊσοδυναμίας κατά την περίοδο πέψης.

Να εκτιμηθούν τα φυσικοχημικά χαρακτηριστικά των περιεχομένων του στομάχου και του ανώτερου λεπτού εντέρου και των αντιστοίχων υδατικών και μικκυλιακών φάσεων, μετά από τη χορήγηση του γεύματος που χρησιμοποιείται για να επάγει την περίοδο πέψης στις μελέτες βιοδιαθεσιμότητας/βιοϊσοδυναμίας (πρότυπο γεύμα).

Να αξιολογηθεί η ανάγκη τροποποιήσεων σε *in vitro* μεθοδολογίες που χρησιμοποιούνται σήμερα για την εκτίμηση της ενδοαυλικής συμπεριφοράς *per os* χορηγούμενων προϊόντων στη διάρκεια της πέψης και συγκεκριμένα: (α) να αξιολογηθεί η επάρκεια της προσομοίωσης των ενδοαυλικών χαρακτηριστικών με τα υγρά μέσα που χρησιμοποιούνται σήμερα στις *in vitro* δοκιμασίες εκτίμησης της ενδοαυλικής συμπεριφοράς *per os* χορηγούμενων φαρμάκων, και (β) να εκτιμηθεί η επάρκεια της *in vitro* προσομοίωσης του ενδοαυλικού περιβάλλοντος με τη χρήση της διάταξης TIM-1.

Μέθοδοι

Οκτώ υγιείς ενήλικοι άνδρες εθελοντές συμμετείχαν σε μια τυχαιοποιημένη, απλής δόσης, δύο φάσεων, διασταυρωτή μελέτη. Το πρότυπο γεύμα, που περιείχε τον μη απορροφούμενο δείκτη ερυθρό της φαινόλης, χορηγήθηκε στο άντρο μέσω ενός ρινο-γαστρο-δωδεκαδακτυλικού σωλήνα. Τα φάρμακα, παρακεταμόλη και δαναζόλη, χορηγήθηκαν υπό μορφή διαλυμάτων (Φάση Ι) και εναιωρημάτων (Φάση ΙΙ) με ένα ποτήρι νερό, 30 min μετά την έναρξη χορήγησης του γεύματος. Δείγματα αναρροφήθηκαν από το άντρο και το ανώτερο λεπτό έντερο για τις επόμενες τέσσερις ώρες. Τα δείγματα αναλύθηκαν για το περιεχόμενο τους σε φάρμακα, ερυθρό της φαινόλης, pH, ρυθμιστική χωρητικότητα, ιξώδες, ωσμωτικότητα, και παρουσία διαλυτοποιητικών παραγόντων.

Στα πειράματα με τη διάταξη TIM-1 προσομοιώθηκε το πρωτόκολλο της κλινικής μελέτης.

Αποτελέσματα

Οι φαινόμενες συγκεντρώσεις στην υδατική φάση των γαστρικών περιεχομένων ήταν υψηλότερες από αυτές στη μικκυλιακή φάση των περιεχομένων του ανώτερου λεπτού εντέρου για την παρακεταμόλη. Το αντίθετο παρατηρήθηκε για τη δαναζόλη. Η γαστρεντερική μεταφορά της παρακεταμόλης (υδατικό διάλυμα ή εναιώρημα) και της δαναζόλης (υδατικό εναιώρημα) θα μπορούσε να περιγραφεί ως μια φαινόμενη πρωτοταξική διαδικασία. Η μεταφορά του λιπιδικού διαλύματος δαναζόλης παρουσίασε πολύ υψηλή διατομική μεταβλητότητα.

Το ιξώδες των περιεχομένων του ανώτερου γαστρεντερικού αυλού ήταν πολύ υψηλότερο από τις τιμές που έχουν αναφερθεί για τη διαπεπτική περίοδο.

Προτάθηκαν νέα μέσα για την προσομοίωση των ενδογαστρικών περιεχομένων και της υδατικής φάσης των ενδογαστρικών περιεχομένων. Η διάταξη TIM-1 προσομοίωσε ικανοποιητικά την παρουσία της παρακεταμόλης (διάλυμα και εναιώρημα) και της δαναζόλης (εναιώρημα) στον ανώτερο γαστρεντερικό αυλό, όχι όμως τις εκκρίσεις στο στόμαχο, την πέψη των λιπών και τα επίπεδα χολικών οξέων στο δωδεκαδάκτυλο.

Συμπεράσματα

Οι συγκεντρώσεις στα περιεχόμενα και στην υδατική/μικκυλιακή φάση των ενδοαυλικών περιεχομένων και οι τιμές των παραμέτρων που διέπουν την κινητική της γαστρεντερικής μεταφοράς των φαρμάκων μετά τη χορήγηση του προτύπου γεύματος περιεγράφηκαν για πρώτη φορά.

Αντιπροσωπευτικές τιμές ιξώδους για τα περιεχόμενα του στομάχου και του ανωτέρου λεπτού εντέρου, καθώς και η σύσταση μέσων για την Επιπέδου II προσομοίωση της υδατικής φάσης των γαστρικών περιεχομένων, μετά το πρότυπο γεύμα, προτάθηκαν για πρώτη φορά.

Τα μέσα προσομοίωσης των ενδογαστρικών περιεχομένων στην περίοδο πέψης θα μπορούσαν να απλοποιηθούν, ενώ η σύσταση του μέσου FeSSIF-V2 επιβεβαιώθηκε ως αντιπροσωπευτική της μικυλλιακής φάσης των περιεχομένων του ανώτερου λεπτού εντέρου. Η διάταξη TIM-1 ίσως αποτελέσει χρήσιμο εργαλείο για πολλές κατηγορίες φαρμάκων στο μέλλον εφόσον υπάρξουν βελτιστοποιήσεις στις συνθήκες που επικρατούν στο γαστρικό και στο νηστιδικό διαμέρισμα.

Summary

Objectives

To quantify the presence in the upper gastrointestinal lumen and understand the gastrointestinal transfer process of highly permeable drugs under conditions simulating the situation after disintegration of immediate release dosage forms administered in bioavailability/bioequivalence studies in the fed state.

To measure the physicochemical characteristics of gastric contents and contents of the upper small intestine and their respective aqueous and micellar phases, after administration of the meal used to induce fed state conditions in bioequivalence/bioavailability studies (standard meal).

To evaluate the need for adjustments in *in vitro* methodologies used to date to assess intraluminal behavior of *per os* administered drug products in the fed state and specifically: (a) to evaluate the sufficiency of simulation of intraluminal characteristics with liquid media used to date in *in vitro* testing of intraluminal behavior of *per os* administered drugs, and (b) to evaluate the competency of the *in vitro* simulation of the intraluminal environment using the TIM-1 model.

Methods

Eight healthy male adult volunteers participated in a randomized, single dose, two-phase, crossover study. The standard meal, containing the non-absorbable marker phenol red, was administered to the antrum via a naso-gastro-intestinal tube. The drugs, paracetamol and danazol, were administered in solution form (Phase I) and in suspension form (Phase II) with a glass of tap water, 30 min after initiation of the meal. Samples were aspirated from the antrum and the upper small intestine over the next four hours. Samples were analyzed for drug content, phenol red content, pH, buffer capacity, viscosity, osmolality, and presence of solubilizing agents.

The clinical study protocol was mimicked in TIM-1 experiments.

Results

Apparent concentrations in the aqueous phase of antral contents were higher than apparent concentrations in the micellar phase of upper small intestinal contents for paracetamol. The opposite was observed for danazol. The gastrointestinal transfer of paracetamol (aqueous solution or suspension) and danazol (aqueous suspension) could be described as an apparent

first-order process. The transfer of the long-chain triglyceride solution of danazol presented high intersubject variability.

The viscosity of contents from the upper gastrointestinal lumen in the fed state was much higher than values reported in the fasted state.

New biorelevant media for the simulation of intragastric contents and the aqueous phase of intragastric contents were suggested. The TIM-1 model simulated adequately the presence of paracetamol (solution or suspension) and danazol (suspension) in the upper gastrointestinal lumen, but not the gastric secretions, the digestion of lipids, and the bile acid levels.

Conclusions

Concentrations in the aqueous/micellar phase of luminal contents and values of parameters controlling drug transfer after the standard meal were reported for the first time.

Representative viscosity values in the stomach and the upper small intestine and Level II composition of the aqueous phase of gastric contents, after the standard meal, were proposed for the first time.

Biorelevant media simulating the intragastric conditions after ingestion of a standard meal could be simplified whereas FeSSIF-V2 composition was confirmed to be representative of the micellar phase of contents of the upper small intestine. The TIM-1 model could be a useful tool in drug development in the future after optimization of conditions in the gastric and jejunal compartments.

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I am indebted to Dr. Konstantinos Goumas, Head of the Department of Gastroenterology, Red Cross Hospital of Athens and principal investigator of the clinical study, for his collaboration, as well as to Aikaterini Lourbakou, Radiologist, and Miranta Kotoglou, Techinician, for their assistance in the intubation procedures. Moreover, I am deeply thankful to the volunteers who participated in the study, without whom the project could not have been realized.

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Last but not least, my gratitude goes to my family and friends for their love, constant encouragement and support.

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Pentafragka C, Vertzoni M, Dressman J, Symillides M, Goumas K, Reppas C. *Characteristics of contents in the upper gastrointestinal lumen after a standard high-calorie high-fat meal and implications for the in vitro drug product performance testing conditions.* Eur J Pharm Sci. 2020, *doi: 10.1016/j.ejps.2020.105535*

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Participation with poster: ***"Population PK/PD modeling of granocyte colony-stimulating factors given as single and repeated doses in healthy volunteers"***

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API	active pharmaceutical ingredient
BA/BE	bioavailability/bioequivalence
C	cholic acid
CHO	cholesterol
DG-O	1,2-dioleyl-rac-glycerol
DG-P	dipalmitin
DGs	diglycerides
egg-PC	phosphatidylcholine from egg yolk
FAs	fatty acids
FeSSGF	fed state simulating gastric fluid
FeSSIF	fed state simulating intestinal fluid
FeSSIF-V2	fed state simulating intestinal fluid – version 2
GC	glycocholic acid
GCDC	glycohenodeoxycholic acid
GDC	glycocholic acid
GHC	glycohyocholic acid
GHDC	glycohyodeoxycholic acid
GI	gastrointestinal
IR	immediate release
LA	linoleic acid
LOQ	limit of quantification
lyso-PC	3-sn-lysophosphatidylcholine
MGs	monoglycerides
na	not available
OA	oleic acid
PC	phosphatidylcholine
SA	stearic acid
TC	taurocholic acid
TCDC	taurochenodeoxycholic acid
TGs	triglycerides
UDC	ursodeoxycholic acid

A. INTRODUCTION

A.1. Clarifications

The following clarifications are relevant to the contents of this thesis. They are also in line with currently applied conditions in oral drug absorption studies (EMA, 2010; FDA, 2019).

Fasted state: The period immediately after a glass of water (~240 mL) until the consumption of the next meal that cannot be earlier than 4 hours after the glass of water. The water should be consumed approximately 12 hours after the last meal.

Drug administration in the fasted state: Together with the glass of water.

Fed state: The period 30 min after the start of consumption of the standard meal until the stomach is practically emptied from meal components. The meal should be consumed approximately 12 hours after the last one.

Standard meal: A high-calorie (800–1000 calories), high fat (approximately 50% of total caloric content) meal which derives approximately 150, 250 and 500–600 calories from protein, carbohydrate and fat, respectively. A standard meal example that has been indicated by major regulatory agencies (EMA, 2010; FDA, 2019) and is frequently employed in drug BA/BE studies performed in the fed state consists of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and a glass of whole milk.

Drug administration in the fed state: 30 min after the start of consumption of the standard meal with a glass of water (~240 mL).

A.2. Disposition of drug products in the upper GI lumen in the fed state

During digestion, a continuous pattern of contractions is observed in the stomach. Tonic contractions move contents downwards (Pal *et al*., 2007). Peristaltic contractions are responsible for the intense grinding and mixing of contents by retropulsion of chyme back into the corpus of the stomach (Schwizer *et al*., 2006). Antropyloric contractions cause the pylorus to partially open and let liquids and particles smaller than 1-2 mm flow into the duodenum (Dressman, 1986; Marciani *et al*., 2001), whereas larger objects are retropelled back into the stomach for further grinding. Large, indigestible solids are retained in the stomach and until the recurrence of Phase III of the Interdigestive Migrating Motor Complex (Newton, 2010; Weitschies *et al*., 2010).

An important determinant of gastric emptying rates of meal components is the amount of ingested calories; it has been reported that, depending on the type of meal and subject's health conditions, it varies between 120-240 kcal/min (Cecil *et al*., 1999; Collins *et al*., 1983; Lyrenås *et al*., 1997).

After ingestion of the standard meal the volume of gastric contents is about 100 mL higher than the volume of the meal and gastric secretory response maintains this volume constant for about 1-1.5 hours, before starting to slowly decrease (Koziolek *et al*., 2014b). It takes about 4-8 hours for the standard meal to completely empty from the stomach (Koziolek *et al*., 2014b). However, it has been reported that water can empty from the stomach in the fed as in the fasted state (Grimm *et al*., 2017; Koziolek *et al*., 2014b; Koziolek *et al*., 2016; Waldeyer, 1908) through a shortcut around the bulk contents via which any ingested water that does not mix with them may empty within a few minutes.

Given the above, after the standard meal, aqueous drug solutions or aqueous drug suspensions will likely slide down the lesser curvature and empty rapidly from the stomach into the duodenum, similarly to water and independently of the meal (Grimm *et al*., 2017; Koziolek *et al*., 2014b). Based on early exposure data, this behavior has been recently confirmed for a paracetamol suspension (Statelova *et al*., 2019). In contrast, solid drug dose units will be deposited in the proximal stomach (e.g. Weitschies *et al*., 2008). Non-disintegrating monolithic products (about 6mm or bigger) will be retained in the stomach and empty as bolus when Phase III of the Interdigestive Migrating Motor Complex occurs (Coupe *et al*., 1991).

To date, data on the drug presence and/or the drug transfer process from the stomach into the duodenum when IR tablets or capsules are administered after the standard meal have been very limited. Early data for capsules collected by using gamma scintigraphy are not useful because the dosing conditions were not controlled (Davis *et al*., 1984) or the fed state protocol (Hunter *et al*., 1983; Theodorakis *et al*., 1980) was much different than that applied in BA/BE studies during the last three decades (Department of Community Services and Health, 1989; EMA, 2010; FDA, 1992, 2002, 2019).

For IR tablets or IR layers of modified release tablets, time for complete disintegration in the human stomach after the standard meal has been reported to range from slightly more than 10 min to about 1 hour (Kelly *et al*., 2003; Rubbens *et al*., 2019; Weitschies *et al*., 2008). For hard gelatin capsules, rupture time after the standard meal is typically slightly longer than 10 min (Digenis *et al*., 2000). As a result, substantial drug concentrations in stomach and drug emptying to the duodenum are not expected immediately after ingestion, whereas during the

disintegration/rupture period the solid and/or dissolved drug is mixed with bulk gastric contents.

A.3. The intraluminal environment in the fed state

The characteristics of the luminal environment have been mainly evaluated after administration of liquid meals (having similar composition, origin of calories, calorie content and/or volume to that of the standard meal). Based on the few studies published to date on the impact of homogenization of solid–liquid meals (having a much lower calorie content than the reference meal) (Grimm *et al*., 2017; Malagelada *et al*., 1979) the extent to which the luminal environment after administration of liquid meals is similar to that after administration of the standard meal is not clear. The composition and caloric content distribution of meals that are similar to the standard meal and have been used to date to explore the physicochemical properties and transit of luminal contents in the fed state are provided in Table A.1.

Median gastric pH values after the standard meal do not differ substantially between studies (Dressman *et al*., 1990; Koziolek *et al*., 2015), but intersubject variability is high (Figure A.1). Homogenization of a solid-liquid meal leads to slightly higher median pH during the first hour but the overall difference was not statistically significant (Figure A.1, Malagelada *et al*., 1979). Importantly, the pH after administration of a homogeneous liquid meal was substantially higher (Figure A.1, Kalantzi *et al*., 2006a).

Other physicochemical characteristics of gastric contents have been measured only after administration of liquid meals (Pentafragka *et al*., 2019). Relevant information is summarized in Table A.2.

In the upper small intestine, only pH has been measured after administration of the standard meal. Dressman *et al*. reported an overall median of pH 6.3 for 60-240 min after the standard meal (Dressman *et al*., 1990). Rubbens *et al*. reported a median of 5.4 for 30-240 min after administration of the standard meal and the weak acid diclofenac (Rubbens *et al*., 2019). Physicochemical characteristics after administration of liquid meals are summarized in Table A.3.

Table A.1: Meals that have been used to explore the physicochemical properties and transit of luminal contents in the fed state

Meal Texture	Meal Composition	Calorie content				Volume (mL)	Reference
		Total (kcal)	Fat (%)	Protein (%)	Carb. (%)		
Standard meal	2 slices of toast with butter, 2 eggs fried in butter, 2 strips of bacon, 4 oz. hash brown potatoes, 240 mL whole milk	800-1000	50 – 75	15 - 19	25 - 31	500	Koziolek *et al*., 2014 Koziolek *et al*., 2015
	6 oz. hamburger, 2 slices of bread, 2 oz. hash brown potatoes, 1 tbsp. ketchup, 1 tbsp. mayonnaise, 1 oz. tomato, 1 oz. lettuce, 8 oz. milk	1000	57	17	26	na	Dressman *et al*., 1990
	2 slices of bread, 40 g cheese, 150 mL orange juice, 150 mL milk, 20 g cereal	511	35	17	48	na	Weitchies *et al*., 2005
	1 slice of toast, 5g butter, 1 egg fried in butter, 1 slice of bacon, 2 oz. hash browns, 120 mL whole milk	460	55	15	30	250	Grimm *et al*., 2017
Solid - liquid and homogenized	90 g tenderloin steak, 0.1 g salt, 25 g white bread with 8 g butter, 60 g vanilla ice cream, 35 g chocolate syrup, 240 mL water	458	40	20	40	400	Malagelada *et al*., 1976 Malagelada *et al*., 1979
Homogenized	80 g string beans, 90 g beef, 70 g fried potatoes, 10 g butter, 15 mL oil	662	63	16	21	700	Carrière *et al*., 2005
	43 mL milk, 57 g whipping cream, 51 g instant chocolate cream, 15 g casein powder, 35 mL water	491	59	18	23	na	Grimm *et al*., 2017
Liquid heterogeneous	50 g olive oil, 1 egg, 20 g sucrose, 5 mL vanilla extract, 250 mL of 0.15 M NaCl, water	604	73	14	13	400	Hernell *et al*., 1990
	70 g olive oil, 1 egg, 1 egg white, 70 g sucrose, 1.8 g NaCl	960	65.5	5.0	29.5	400	Armand *et al*., 1996
	62.5 g olive oil, 1.25 eggs, 25 g sucrose, 2.7 g NaCl, vanilla flavor, water	750	73	14	13	500	Vertzoni *et al*., 2012
Liquid homogeneous	Ensure® Plus	753	32	27	41	500	Kalantzi *et al*., 2006
		602	32	27	41	400	Clarysse *et al*., 2009 Riethorst *et al*., 2014
	Scandishake® Mix	598	46	8	46	300	Clarysse *et al*., 2009

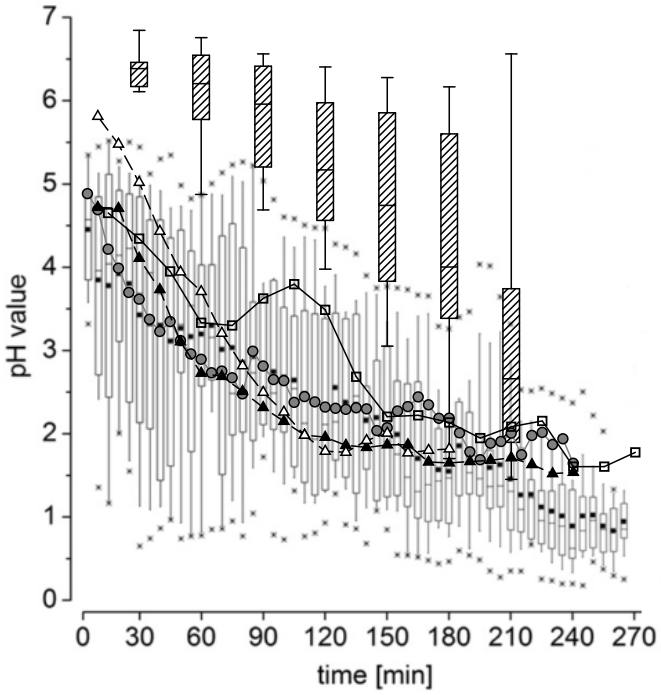

Figure A.1. Gastric pH-time profiles after administration of meals with different texture based on data from various studies: (Koziolek *et al*., 2015) standard meal (empty boxplot; asterisks: max/min); (Dressman *et al*., 1990) standard meal (● ; median values); (Malagelada *et al*., 1979) solid-liquid meal (▲; mean values); (Malagelada *et al*., 1979) homogenized solid-liquid meal (Δ ; mean values); (Kalantzi *et al*., 2006a) homogeneous liquid meal (lined boxplot); (Rubbens *et al*., 2019) standard meal and the weak acid diclofenac (□ ; mean values).

Table A.2: Physicochemical characteristics and composition of gastric contents at various times after meal (Table A.1) administration to fasted adults.

	0.5h	**1h**	**2h**	**3h**	**4h**
pH	3.6 - 4.1	2.7 - 3.3	2.0 - 2.3	1.5 - 2.2	0.7 - 1.6
Buffer capacity (mmol/L/ΔpH) (HCl titration)	25	23	23.2	29.8	na
Osmolality (mOsm/kg)	531	474	442	321	na
Bile salts (mM)	<LOQ				
Phospholipids (mM)	na	2.9	1.9	0.9	0.4
CHO (mM)	na	1.2	1.2	0.7	0.4
FAs (mM)	na	9.4	14.0	15.3	7.3
MGs (mM)	na	2.5	3.2	4.6	1.1
DGs (mM)	na	8.2	17.7	13.5	9.1
TGs (mM)	na	157.1	150.4	154.0	42.7

Range of median values for pH, mean values for all other parameters; na: not available

pH data after administration of solid-liquid meals are from: Malagelada *et al*., 1979; Dressman *et al*., 1990; Koziolek *et al*., 2015. Buffer capacity, osmolality, bile salts (LOQ: 500 µM) data are from Kalantzi *et al*., 2006a. Lipid species data are from Armand *et al*., 1996.

Table A.3: Physicochemical characteristics and composition of contents of the upper small intestine at various times after meal (Table 1) administration to fasted adults.

	30 min	1 h	2 h	3 h
pH	6.2 - 6.6	6.3 - 6.5	5.3 - 6.1	5.6 - 5.8
Buffer capacity (mmol/ L/ ΔpH) (HCl titration)	28	22 - 27.4	18 - 23.3	12 - 25.6
Osmolality (mOsm/ kg)	291 - 391	360 - 402	274 - 423	215 - 364
Bile salts (mM)	10.1 - 14.0	5 - 18.2	3.9 - 7.7	3.7 - 7.3
Phospholipids (mM)	3.9 - 6.0	2.87 - 7.1	1.5 - 5.6	1.4 - 4.3
CHO (mM)	0.75 - 1.50	0.68 - 3.12	0.40 - 1.2	0.30 - 1.4
FAs (mM)	30.2 - 52.0	21.7 - 54	42 - 46	34.7 - 56.9
MGs (mM)	5.9 - 9	7.08 - 11	5.21 - 9.6	4.20 - 18.4
DGs (mM)	1.1 - 6.5	1 - 10.7	4.20 - 12.6	2.6 - 33.7
TGs (mM)	1.16 - 4.7	0.76 - 60.7	1.90 - 44.7	0.60 - 63.3

Range of median values for pH, range of mean values for all other parameters; na: not available

Data from: Hernell *et al*., 1990; Armand *et al*., 1996; Kalantzi *et al*., 2006a; Kalantzi *et al*., 2006b; Clarysse *et al*., 2009 ; Vertzoni *et al*., 2012; Riethorst *et al*., 2015

A.4. *In vitro* drug testing conditions in the fed state

In vitro methodologies for the evaluation of oral drug products in the upper GI lumen in the fed state have been developed and, in some cases, in combination with physiologically based pharmacokinetic modelling techniques, they have succeeded in reproducing the average plasma profiles after drug product administration and/or understanding the mechanism(s) of observed food effects on oral drug absorption (Pentafragka *et al*., 2019).

When using compendial Apparatus combined with biorelevant media simulating the fed state intraluminal environment, the simulation of luminal characteristics has been predominantly based on the data collected after administration of liquid meals (Markopoulos, Andreas *et al*., 2015). Media with increasing level of simulation accuracy have been proposed: Level 0 media are simple buffers with physiologically relevant pH; Level I media have the pH and the buffer capacity adjusted to physiologically relevant values; Level II media have adjusted osmolality to physiologically relevant values and incorporate bile components, dietary lipids and digestion products, to reflect the solubilization capacity of lipid species present in luminal fluids and the major differences between the fasted and fed state conditions; Level III media represent the higher and most complex level of simulation, aiming to account for the effects of proteins, enzymes or viscosity. Indicative compositions of media simulating the fed stomach and fed upper small intestine are presented in Table A.4.

Importantly, in *in vitro* methodologies proposed to date, certain luminal characteristics which could potentially affect product performance and/or drug absorption, e.g. luminal viscosity and composition of the micellar phase in the upper small intestine have not been adequately addressed.

In addition to compendial Apparatus, *in vitro* models that address the dynamic nature of luminal conditions in the fed state and potentially account for the intraluminal hydrodynamics and digestion, have been proposed. Examples include the Dynamic Gastric Model (Wickham *et al*., 2012); the Fed stomach model (Koziolek *et al*., 2014a); and the TIM gastrointestinal systems (Minekus, 2015).

To date, the usefulness of some of these *in vitro* methodologies has been evaluated indirectly e.g. by evaluating whether *in vitro* differences in formulation performance are reflected on differences in the average values of key pharmacokinetic parameters (e.g. (Blanquet *et al*., 2004; Schick *et al*., 2020; Souliman *et al*., 2006; Verwei *et al*., 2016); or by evaluating whether *in vitro* data are useful in informing physiologically based pharmacokinetic models for simulating the average plasma profiles (e.g. (Jamei *et al*., 2020; Nicolaides *et al*., 2001; Pandey *et al*., 2014)). Direct comparisons of biorelevant *in vitro* data with human luminal data in the fed state are lacking. To increase the usefulness of *in vitro* data (including potential regulatory applications), efforts should be taken to optimize the existing or develop and systematically validate new *in vitro* methodologies that are representative of the luminal conditions but not unnecessarily complex. Direct comparisons of *in vitro* data with human luminal data after the standard meal could allow for characterizing situations where extensive simulation of the dynamic nature of the conditions for the evaluation of drug product performance in the fed state may not be needed.

For the *in vitro* data to reliably support decisions on the potential impact of food on drug product performance, better understanding of the system is needed. e.g. how the drug empties from the stomach after the standard meal and what is the environment in the upper GI lumen after the standard meal.

Table A.4: Level I and Level II simulation of composition of contents of the upper GI lumen in the fed state (Markopoulos, Andreas *et al*., 2015).

	FeSSGF$_{early}$	**FeSSGF$_{middle}$**	**FeSSGF$_{late}$**	**FeSSIF-V2**
Lipofundin (%v/v)	**18** *	**9** **	**4.5****	**-**
Sodium taurocholate (mM)	**-**	**-**	**-**	**10**
Lecithin (mM)	**-**	**-**	**-**	**2**
Glyceryl monooleate (mM)	**-**	**-**	**-**	**5**
Sodium oleate (mM)	**-**	**-**	**-**	**0.8**
Sodium chloride (mM)	**270.1**	**181.7**	**127.5**	**125.5**
Acetic acid (mM)	-	18.31	-	-
Sodium acetate (mM)	-	32.98	-	-
Ortho-phosphoric acid (mM)	-	-	5.5	-
Sodium dihydrogen phosphate (mM)	-	-	32	-
Maleic acid (mM)	47.0	-	-	71.9
Sodium hydroxide (mM)	-	-	-	102.4
Osmolality (mOsm/kg)	**559**	**400**	**300**	**390**
Buffer capacity [(mmol/L)/ΔpH]	21	25	25	25
pH	6.4	5.0	3.0	5.8

Level I simulation of media composition results after eliminating data with bold characters; FeSSGF$_{early}$: fed state simulating gastric fluid 0-75 min after ingestion; FeSSGF$_{middle}$: fed state simulating gastric fluid 75-165 min after ingestion; FeSSGF$_{late}$: fed state simulating gastric fluid >165 min after ingestion; FeSSIF-V2, fed state simulating intestinal fluid in upper small intestine, version 2

* Equivalent to 17.5 g ** Equivalent to 8.75 g *** Equivalent to 4.375 g

A.5. Aims of the Thesis and justification of the applied methodology

Considering the very limited data describing the intraluminal fate of orally administered drugs and the GI environment after the standard meal, the need for a clinical study to collect gastric and upper small intestinal samples after the standard meal was raised.

A human aspiration study for evaluating drug product performance and characterizing luminal contents' composition after administration of the standard meal is challenging. The drugs must be administered safely after the positioning of the gastro-intestinal aspiration tube and 30 min after the initiation of meal intake. Another concern relates to the tube passing through the pylorus; it should not restrict the drug transfer process into the duodenum and it should not create difficulties in aspirating samples from the upper small intestine which may contain drug and meal solid particles and/or have increased viscosity. To address these issues, the standard meal was homogenized, after addressing the impact of homogenization on the viscosity and size of meal particles, so that the meal and drugs were administered directly into the antrum

by using a tube that allows aspirating samples from the stomach and the upper small intestine without restricting the physiological GI transfer process.

This Thesis had three specific objectives.

A.5.1. Objective #1

The first objective was to measure the total drug amount per volume of contents aspirated from the stomach and from the upper small intestine, as well as the apparent drug concentrations in the aqueous phase of contents aspirated from the stomach and in the micellar phase of contents aspirated from the upper small intestine, at various times after administration of drug solutions and suspensions to the antrum, i.e. under dosing conditions simulating the situation after disintegration of orally administered IR dosage forms in BA/BE studies. Based on the total drug amounts per volume of intraluminal contents, the aim of understanding the GI drug transfer process was also set.

Two model highly permeable drugs were employed; paracetamol and danazol.

Paracetamol is a weak inhibitor of prostaglandin biosynthesis in the central nervous system, with analgesic, antipyretic and weak anti-inflammatory action. Paracetamol ($C_8H_9NO_2$) with pKa 9.5, acidic, is a white crystalline powder with a molecular weight of 151.2 g/mol and a melting point of about 169 °C. Paracetamol half-life in plasma is 1-4 hours (SPC PANADOL 500 mg). Initially, paracetamol was classified as a BCS Class III molecule, i.e. as a molecule with high solubility and low permeability (Kalantzi *et al*., 2006). However, following a technical report by the World Health Organization (WHO) panel of experts on medicinal product specifications, it is classified as a Class I BCS molecule. The permeability criterion was reduced from 90% in the FDA Guidelines to 85% in the cross-sectional document; therefore at a dose of 500 mg paracetamol is a BCS Class I molecule (WHO, 2006).

Danazol is a synthetic steroid derivative of ethisterone, mainly used to treat endometriosis and fibrocystic mastopathy. According to the National Organization for Medicines, the most common dosage of danazol for the indication of endometriosis is set at 200 to 800 mg and for the indication of fibrocystic mastopathy at 200-400 mg daily. Danazol is commercially available in 100 and 200 mg capsules (National Prescription 2007). Danazol ($C_{22}H_{27}NO_2$), neutral molecule, is a crystalline white to pale yellow powder with a molecular weight of 337.5 g/mol and a melting point of about 225°C. Danazol half-life in plasma is 3-6 hours (SPC DANATROL 100 mg). It is a BCS Class II poorly soluble, highly permeable molecule and has a positive food effect (Tsume *et al*., 2014)

To evaluate GI water flux, phenol red was added into the standard meal. Phenol red or phenolsulfonphthalein ($C_{19}H_{14}O_5S$) is a dark red crystalline powder with a molecular weight of 354.4 g/mol and a melting point of about 300 °C. It is commonly used as a pH indicator, having a yellow color at a pH of 6.4 or below and a red color at a pH of 8.2 and above. It can also be used as a qualitative indicator of GI transit time and a quantitative indicator of luminal secretions. It is a water-soluble molecule, non-absorbable in the studied part of the GI tract, biologically inactive, and non-toxic in the concentrations and total amounts used in the study (French *et al*., 1968; Wiggins and Dawson, 1961).

A.5.2. Objective #2

The second objective was to physicochemically characterize of the upper GI environment after administration of the standard meal. Since the model drugs employed are non-ionisable at physiological pH values, they are expected to have minimal, if any, effects on the physicochemical characteristics of luminal contents (Litou *et al*., 2020).

Specifically, the pH, buffer capacity, lipid content, and bile acid content in aspirated samples were measured. As mentioned above, apart from the gastric pH, relevant data in adults have only been published after administration of liquid meals, but not after the standard meal itself.

The viscosity of contents in the stomach and in the upper small intestine was also measured for the first time in the fed state in humans.

The osmolality, the lipid content and the bile acid content of the aqueous phase of gastric contents and of the micellar phase of contents of the upper small intestine were also assessed. Relevant data in adults, after the standard meal, have not yet been published.

A.5.3. Objective #3

The third objective was to investigate the potential implications of the collected information from the clinical study on the *in vitro* drug testing conditions for oral drug product performance in the fed state. Specifically:

- The compositions of currently used fed state simulating media (Markopoulos, Andreas *et al*., 2015) were revisited, and

- The usefulness of TIM-1 (The TIM company, Zeist, Netherlands) in reproducing human drug disposition data and characteristics of contents in the upper GI lumen after the standard meal, was evaluated by mimicking the clinical protocol in TIM-1 runs. TIM-1 is a multi-compartmental dynamic model developed in the early 1990s as a physiologically relevant digestion model in

food sciences (Helbig *et al*., 2013; Minekus *et al*., 2005; Minekus *et al*., 1995; Reis *et al*., 2008) but its use has been extended to the pharmaceutical field to study oral drug product performance (Blanquet *et al*., 2004; Verwei *et al*., 2016). TIM-1 mimics the upper and middle GI tract, comprising four serial compartments simulating the stomach, duodenum, jejunum and ileum. It simulates biliary and pancreatic secretions, lipid digestion, controls luminal pH and accounts for absorption through removing of drug via filtration from the jejunal and ileal compartments.

B. EXPERIMENTAL PART

B.1. Materials

B.1.1 Instruments

- Analytical balance KERN PCB1000-2, Kern & Sohn GmbH (Germany)
- Analytical precision balance KERN ABT 120-5 DNM, Kern & Sohn GmbH (Germany)
- Amber glass vials 4.5 mL (45 x 14.75 mm), CleanPack® Laboratory Chemical Packing (USA)
- Columns BDS Hypersil™ C18 (250 x 4.6 mm, 5µm) ThermoFischer Scientific (USA)
- Columns BDS Hypersil™ C18 (150 x 3.0 mm, 5µm) Fortis™ Technologies (UK)
- Cone and plate rotational viscometer (RM 100 CP 2000 PLUS, LAMY Rheology, France)
- Double lumen, naso-gastro-intestinal tube Freka® Trelumina, Freka Trelumina Ch/Fr 16/9, 150 cm, ref no. 7550911, Fresenius Kabi Deutschland Gmbh (Germany).
- Food processor: Multi Pyrex SB-223. PYREX® (France)
- High Performance Liquid Chromatography System consisting of a Spectra System P1000 pump, a UV-visible Spectra System UV1000 detector, an AS3000 autosampler, a Spectra System SN4000 controller, and the software ChromQuest® (ChromQuest Inc., San Jose, USA)
- High Performance Liquid Chromatography System consisting of a Spectra System P4000 pump (ThermoQuest Inc., San Jose, USA), a charged aerosol detector, CAD, ESA Corona®, ESA, Chemfold, MA, USA), an AS3000 autosampler (ThermoQuest Inc., San Jose, USA), and the software EZChrom Agilent® version 3.2 (Agilent Technologies, Inc., Santa Carla, CA, USA)
- High Performance Liquid Chromatography System UltiMate 3000 Series, consisting of an LPG-3400SD Pump, a WPS-300SL autosampler, a VWD-3100 UV/visible photometer and the software Chromeleon™ 7.2 SR5 (Thermo Scientific™, Thermo Fisher Scientific, Waltham, MA, USA)
- Laboratory sieves, 200 mm outer diameter, 2 mm and 1mm mesh opening, Endecotts Ltd., UK
- Magnetic stirrer plate model RH basic, IKA® works, Inc. (USA)
- Osmometer, model Semimicro Typ Dig. L, KNAUER GmbH (Germany)
- Particle size analyzer with laser beam diffraction (Malvern Mastersizer S, Malvern Panalytical Ltd, UK).
- pH meter Schott, model CG842, SCHOTT GLAS (Germany)
- Precolumns BDS Hypersil™ C18 (10 x 4 mm, 5µm) ThermoFischer Scientific (USA)
- Sterile plastic insulin syringes 1 mL, Pic solution (Pikdare S.r.I., Italy)

- Sterile plastic disposable syringes 5 mL, 10 mL and 20 mL, BMDI Bio Medical Distribution Integrity (China)
- Sterile syringes 50 (60) mL Catetere Exelmed, I.M.I.snc, Montegrotto Terme PD, Italy
- Thermostatic centrifuge Universal 32 R, Hettich Zentrifugen (Germany)
- Thermostatic centrifuge Universal 320 R, Hettich Zentrifugen (Germany)
- Ultracentrifuge (Ultra-Pro 80, Serial No. 9802745, Sorvall, USA)
- Ultracrimp 11.5 mL ultracentrifuge tubes (Thermo Fisher Scientific, USA)
- Ultrasonic bath, Elmasonic S100H, Elma Schmidbauer GmbH (Singer, Germany)
- Vortex model MS2 minishaker, IKA® works, Inc., (USA)

B.1.2. Standard meal ingredients

- 2 slices of toasted bread. Καραμολέγκος® Σταρένιο (per slice: 63 kcal, 0.7 g fat, 11.7 g carb., 2.2 g protein)
- 2 eggs. Χρυσά Αυγά® , size L (per egg: 92 kcal, 7.4 g fat, 0.67 g carb., 8.7 g protein)
- 2 strips bacon. NIKAS®, smoked bacon (per strip: 50 kcal, 4 g fat, 0.7 g carb., 2 g protein
- 1 glass i.e. 250 mL whole milk. ΔΕΛΤΑ® (per glass: 158 kcal, 8.8 g fat, 11.5 g carb., 8 g protein)
- 10 g butter. LURPAK® (per 100g: 747 kcal, 82 g fat, 0.7 g carb., 0.6 g protein)
- 50 g fried potatoes. Everest® (per 100 g: 336 kcal, 20.6 g fat, 44 g carb., 4 g protein)
- Sunflower oil. Μαράτα® (per 100 mL: 828 kcal, 92 g fat, 0 g carb., 0 g protein)

B.1.3. Active Pharmaceutical Ingredients

- Danazol, 17α-Ethynyl-17β-hydroxyandrost-4-en-[2,3-d]isoxazole, USP, micronized powder. Mean particle size 6.75 μm. Purity: 99,7%. Batch No. 5201-B-17009. Manufactured by Coral Drugs Pvt. Limited, INDIA. Supplied by Pharmaten, GREECE.
- Paracetamol, N-(4-hydroxyphenyl)acetamide, micronized powder. Purity 99,8%. Batch No. CW-1704010M. Manufactured by Lianyungang Kangle Pharmaceutical Co., Ltd, CHINA. Supplied by Unipharma, GREECE.

B.1.4. Reagents

- Acetic acid, glacial (CH_3COOH) 100% Merck KGaA, Darmstadt, Germany
- Acetonitrile, HPLC grade. Chromasolv® Plus. Honeywell | Riedel-de Haën (Germany) Acetonitrile, LC-MS hypergrade. LiChrosolv® Merck KGaA, Darmstadt, Germany
- Acetophenone. (Sigma-Aldrich Chemie GmbH (USA) 42163-1mL, CAS 98-86-2)
- Ammonium formate ≥ 97% (Fluka®Analytical, Sigma-Aldrich Chemie GmbH (USA) 09739-100g, CAS 540-69-2)
- Cholesterol oleate (Sigma-Aldrich Chemie GmbH (USA) C8667 - 5g, CAS 57-88-5)

- Diethyl(p-nitroethyl)phosphate (paraoxon-ethyl) (Sigma-Aldrich Chemie GmbH (USA) D9286-1g, CAS 311-45-5)
- Diisopropylfluorophosphate. (Sigma-Aldrich Chemie GmbH (USA) D0879-1g, CAS 55-91-4)
- 1,2 dioleoyl-rac-glycerol (Sigma-Aldrich Chemie GmbH (USA) D8394 - 100mg, CAS 2442-61-7)
- Dipalmitin (Sigma-Aldrich Chemie GmbH (USA) D2636 - 100mg, CAS 26657-95-4)
- Formic acid 98-100% (Sigma-Aldrich Chemie GmbH (USA) 33015-1L, CAS 64-18-6)
- Glycochenodeoxycholic acid (Sigma-Aldrich Chemie GmbH (USA) 50534 - 250 mg, CAS 16564-43-5)
- Glycocholic acid (Sigma-Aldrich Chemie GmbH (USA) G2878 - 1g, CAS 475-31-0)
- Glycodeoxycholic acid (Sigma-Aldrich Chemie GmbH (USA) G9910 - 1g, CAS 16409-34-0)
- Glycohyocholic acid (Cayman Chemical (USA) 22670 - 10 mg, CAS 32747-08-3)
- Glycohyodeoxycholic acid (Cayman Chemical (USA) 22643 - 10 mg, CAS 13042-33-6)
- Glyceryl trioleate (Sigma-Aldrich Chemie GmbH (USA) T7140 – 1g, CAS 122-32-7)
- Glyceryl trilinoleate (Sigma-Aldrich Chemie GmbH (USA) T9517 – 1g, CAS 537-40-6)
- Hydrochloric acid (HCl) (Sigma-Aldrich Chemie GmbH (USA) 30721-2.5L, CAS 7647-01-0)
- Linoleic acid (Sigma-Aldrich Chemie GmbH (USA) L1376 - 1g, CAS 60-33-3)
- Lyso-phosphatidylcholine (Sigma-Aldrich Chemie GmbH (USA) 62962 - 250mg)
- Methanol, HPLC grade. Chromasolv® Plus. Honeywell | Riedel-de Haën (Germany) Methanol, LC-MS hypergrade. LiChrosolv® Merck KGaA, Darmstadt, Germany 1-monooleyl-rac-glycerol (provided by Danisco A/S (Denmark), 173403-2202/76)
- Oleic acid (Sigma-Aldrich Chemie GmbH (USA) O1008 - 1g, CAS 112-80-1)
- Orthophosphoric acid (H_3PO_4) (code O/0450/P515, Fischer Scientific, UK)
- Perchloric acid 70-72% (CAS 7601-30-3) Honeywell Fluka™ (USA)
- Phenol red/Phenolsulfophthalein (PSP) sodium salt (Sigma-Aldrich Chemie GmbH (USA) P5530 - 25g, CAS 34487-61-1)
- Phenyl-boronic acid. (Sigma-Aldrich Chemie GmbH (USA) 78181-10g, CAS 98-80-6)
- Phosphatidylcholine (provided by Lipoid GmbH (Germany), 790431-6)
- Potassium di-Hydrogen Phosphate (KH_2PO_4) ≥ 99.5% (CAS 7778-77-0, AppliChem GmbH, Darmstadt, Germany)
- Propanol-2, gradient grade for liquid chromatography. LiChrosolv® Merck KGaA, Darmstadt, Germany (CAS 67-63-0)
- Sodium hydroxide (NaOH) ≥ 98% (CAS 1310-73-2) Honeywell Fluka™ (USA)
- Stearic acid (Sigma-Aldrich Chemie GmbH (USA) 85679 - 5g, CAS 57-11-4)
- Taurochenodeoxycholate acid (Sigma-Aldrich Chemie GmbH (USA) T6260 - 250 mg, CAS 6009-98-9)

- Taurocholic acid (Sigma-Aldrich Chemie GmbH (USA) T4009 - 1g, CAS 345909-26-4)
- Triethylamine >99% (Sigma-Aldrich Chemie GmbH (USA) T0886-100 mL, CAS 121-44-8)
- Ursodeoxycholic acid (Sigma-Aldrich Chemie GmbH (USA) U5127 - 1g, CAS 128-13-2)
- Water, HPLC grade. Chromasolv® Plus. Honeywell | Riedel-de Haën (Germany)
- Water, LC-MS hypergrade. LiChrosolv® Merck KGaA, Darmstadt, Germany

B.1.5. Software

- Phoenix WinNonlin 8.2 (Certara USA, Inc., Princeton, USA)
- SigmaPlot® 2000, SPSS Inc., Chicago, IL, USA

B.1.6. TIM-1 experiments

- The TIM-1 Gastrointestinal Model (The TIM Company, Zeist, The Netherlands)
- High Performance Liquid Chromatography Systems Agilent® (Agilent Technologies, Inc., Santa Carla, CA, USA) and the software Empower®3 (Waters™, UK)
- Ultracentrifuge (Sorvall™ WX+, Ultra Series, Thermo Scientific™, Thermo Fisher Scientific, Waltham, MA, USA)
- Pancreatin from porcine pancreas (Sigma-Aldrich, Gillingham, UK)
- Pepsin from porcine gastric mucosa (Sigma-Aldrich, Gillingham, UK)
- Lipase from *Rhizopus oryzae* (Sigma-Aldrich, Gillingham, UK)
- Amylase from *Bacillus sp.* (Sigma-Aldrich, Gillingham, UK)
- Trypsin (Sigma-Aldrich, Gillingham, UK)
- Porcine bile was from Triskelion (Hendrix Slaughter House, Druten, Netherlands)
- The high-calorie, high-fat meal employed in TIM-1 was from Triskelion (Hendrix Slaughter House, Druten, Netherlands). It was based on the standard meal composition (FDA, 2019) and consisted of toast with margarine, bacon, eggs, fried potatoes and whole milk.
- Gastric electrolyte solution (GES) was prepared by dissolving 8 g/L sodium chloride, 1.7 g/L potassium chloride and 0.16 g/L calcium chloride di-hydrate in water. HPMC 0.4% and bile 0.04% gastric solution was prepared by dissolving 0.4 g/L bile extract in water, subsequently adding 4.0 g/L HPMC and stirring the solution overnight. Gastric enzymes solution contained 3 mL of 0.1 M sodium acetate buffer pH 5.0, 6000 units lipase from *Rhizopus oryzae* as an alternative to gastric lipase, 1440000 units pepsin, 42000 units amylase and 299 mL GES.
- Small intestinal electrolyte solution (SIES) was prepared by dissolving 7 g/L sodium chloride, 0.35 g/L potassium chloride and 0.1 g/L calcium chloride di-hydrate in water and adjusting the pH to 7.0 with 1 M sodium hydroxide.
- Pancreatic solution was prepared by dissolving pancreatin powder in water, centrifuging the solution for 20 min at 12.500 G at 4^{o}C and using the supernatant for the experiment

- The bile solution consisted of 100% v/v filtered pig bile

B.2. Methods

B.2.1. The clinical study

B.2.2.1. Clinical center, approvals and study design

The clinical study was performed at the Red Cross Hospital of Athens under a bilateral agreement between the National and Kapodistrian University of Athens and the Hospital (AP 047492/13-6-2018), after receiving approval by the Scientific and the Executive Committee of the Hospital (AP 20505/13-09-17) and according to the currently applied EU regulations (EMA, 2001). The study was also approved by the independent external expert responsible for the *in vivo* studies that took place within the PEARRL programme. Copies of the hospital approvals, as well as a copy of the certificate of insurance of investigators and volunteers, are given in Appendix I. The clinical study was completed in 13 months (January 13th 2018 - February 2nd 2019). It was a randomized, single dose, crossover, two-phase study.

Phase 1: 30 min after initiation of meal administration, paracetamol aqueous solution and danazol sunflower oil solution were administered with a glass of tap water.

Phase 2: 30 min after initiation of administration of the meal, paracetamol aqueous suspension and danazol aqueous suspension were administered with a glass of tap water.

Paracetamol and danazol were administered in single doses equal to/less than the usual single doses administered in clinical practice. According to the literature no interaction is expected between paracetamol and danazol and thus, for ethical reasons, the two APIs were co-administered.

Eight healthy male adult volunteers participated in the study. Each volunteer visited the Gastroenterology Department of the Red Cross Hospital of Athens twice. The rinsing period, between the two consecutive visits, was at least one week i.e. much longer than 7 half-lives of the two APIs in plasma. Each visit lasted about 6 hours. Three days before each visit the volunteer stopped taking any medication and consuming alcohol, and started abstaining from smoking. At 8:00 pm on the last day before each phase the volunteer started fasting. Water intake was allowed *ad libitum* until arrival at the hospital. At each visit an elastic naso-gastro-intestinal tube was placed under radioscopic control. Sixteen visits took place in total.

B.2.2.2. The standard meal

B.2.2.2.1. Meal preparation

The meal ingredients were bought from the local market the day before the experiment. The eggs and bacon were cooked in butter the morning of the experimental day. French fries were bought from Everest® fast food chain just before arriving to the hospital. Just before administration, the meal was homogenized using a Multi Pyrex® food processor. 100 mg phenol red were dissolved in 50 mL water the previous night. The 0.2% aqueous phenol red solution was added to the mixture.

The 18.5 g sunflower oil used to prepare the danazol solution derived 165 kcal that were taken into account in the total calories delivered with the meal. The amount of butter added in the meal was calculated based on the remaining calories, to reach the 990 kcal and 61% fat required. In Phase II, where danazol is suspended in water, the 18.5 g sunflower oil were added in the meal.

Composition and caloric breakdown of the administered meal are presented in Table B.1.

B.2.2.2.2. Impact of homogenization on the texture of the meal

The impact of homogenization on meal's texture was evaluated by comparing the particle size distribution and the viscosity of the meal, after homogenization with Multi Pyrex® food processor (3 meal preparations) and after chewing (3 adult volunteers chewed the meal within 20 minutes and collected it back instead of swallowing).

For the particle size measurements, the total volume of the meal was initially measured. The meal was then let pass sequentially through a 2 mm mesh diameter and a 1 mm mesh diameter sieve. The volume of meal with particles larger than 2 mm, between 1 and 2 mm, and less than 1 mm was estimated. A sample from the latter portion of the meal was transferred in a Malvern Mastersizer S particle size analyzer (Malvern Panalytical Ltd, UK) where the particle size distribution was measured. The detailed method for the particle size analysis is listed in Appendix III.

Meal viscosity was measured using a cone and plate rotational viscometer (RM 100 CP 2000 PLUS, LAMY Rheology, France) at ascending shear rates of 50 s^{-1}, 100 s^{-1} and 200 s^{-1}, at two 25°C and 37°C. The detailed method for the particle size analysis is listed in Appendix III.

The homogenized meal was also characterized physicochemically in terms of mass, pH, buffer capacity, osmolality and surface tension.

Table B.1. Composition and caloric breakdown of the standard meal.

		Distribution and amount of calories (kcal)			
Ingredient	**Quantity**	**Fats**	**Carbohydrates**	**Proteins**	**Total**
Toasted bread	2 slices	13	94	18	125
Eggs	2, size Large	110	5	70	185
Bacon	2 strips	74	6	18	98
Fried potatoes	50 g	72	88	8	168
Whole milk	250 mL	79	46	33	158
Butter	10 g	90	-	-	90
Sunflower oil	16 g	165	-	-	165
Total amount of calories (% of total amount)		603 (61%)	239 (24%)	147 (15%)	989 (100%)

B.2.2.3. Preparation and administration of drug solutions and suspensions

Phase I - Solutions

500 mg paracetamol were weighted and transferred in a glass vial. 40 mL water were added and the solution was mildly stirred on a magnetic stirrer plate at room temperature.

100 mg danazol were weighted and transferred in a glass vial. 16 g sunflower oil were added and the mixture was stirred on a magnetic stirrer plate with slight temperature elevation. Thermal degradation is not expected for danazol (Kulkarni and Nawathye, 2015).

The solutions were prepared the night previous to the experimental day. They were administered to the volunteers with 20 mL syringes via the naso-gastro-intestinal tube. Another 2.5 g sunflower oil were used to wash the danazol container and syringe. The remaining 160 mL water of the total 250 mL of the glass of water (minus the 50 mL in the meal were phenol red was dissolved; minus the 40 mL for the paracetamol solution) were used to wash the paracetamol container and the syringe.

Phase II - Suspensions

500 mg paracetamol were weighted and transferred in a plastic vial the night before the experimental day.

100 mg danazol were weighted and transferred in a glass vial the night before the experimental day.

Right before administration to the volunteers, 10 mL water were added to each of the containers, the powders were suspended by hand shaking and administered to the volunteers with 20 mL syringes via the naso-gastro-intestinal tube. The remaining 200 mL water of the 250 mL of the glass with which drugs should be administered (minus the 50 mL in the meal were phenol red was dissolved) were used to rinse the containers and syringes.

B.2.2.4. Volunteers

Eight healthy male adult volunteers were required to participate in the study. It has been reported in the literature that in the fed state, differences have been observed in the past to the gastric emptying rate between men and women who are menstruating. To restrict variability in gastric emptying, all participants were men (Brennan *et al*., 2009; Caballero-Plasencia *et al*., 1999; Wald *et al*., 1981). Any person who responded positively to the relevant call for expression of interest was called for an interview, where they were informed about the study details and were asked questions on their general health status. Those still willing to participate and seemed suitable for volunteers were checked for their health status by a general physical examination and a blood test.

Inclusion Criteria: Willingness of the subject to participate was indicated by his signed informed consent, age 18 - 60 years, weight within 15% of ideal body weight as determined by Metropolitan Life Tables, verification of suitability by a general physical examination and ability to abstain from smoking, alcohol, and over-the-counter and prescription medication(s) for 3 days prior to and throughout the experimental day. In addition, a blood sample was taken to assess electrolyte balance, kidney and liver function, blood morphologic characteristics, and lipid levels. The subject had to be found healthy in all of these examinations to qualify.

Exclusion Criteria: The existence of a major health problem and/or existence of any condition requiring prescription drug therapy, recent history of GI symptoms regardless of the severity, receipt of an investigational agent (new or generic) within 30 days prior to the initiation of the study, presence of antibodies indicating active acute or chronic HIV, HBV, or HCV infection, use of medication that may affect GI function (including antibiotics) within 30 days of the study and irregular bowel habits were exclusion criteria.

Ten healthy male adult volunteers were recruited according to the inclusion and exclusion criteria. Two subjects were eliminated because, during their first visit, one could not be intubated for reasons relating to the anatomy of the nasal cavity/stomach and another decided to terminate his participation immediately after administration of the meal for personal reasons. Eight healthy male adult volunteers completed both phases of the study. Subjects

were between 21 and 48 years old and deviated by not more than 11% from their ideal body mass index.

B.2.2.5. The naso-gastro-intestinal tube for aspirating samples from the stomach and the small intestine

As in previous aspiration studies performed in our laboratory in the fasted state (Kourentas *et al*., 2016b; Psachoulias *et al*., 2011), a sterile Freka Trelumina Ch/Fr 16/9, 150 cm, two lumen naso-gastro-intestinal tube was used for aspirations both from the antrum and the upper small intestine. The outside diameter (OD) of the gastric lumen of the tube is 5.3 mm and the inside diameter (ID) is 4.1 mm. The gastric lumen of the tube contains the intestinal tube and the thickness of the ring through which samples from the contents of the antrum were aspirated is 0.6 mm. The intestinal lumen of the tube (passing through the pylorus) has an OD of 2.9 mm and an ID of 1.9 mm. Longstreth *et al*. (Longstreth *et al*., 1975) have shown that a 4 mm OD transpyloric tube does not significantly affect gastric emptying of contents after administration of a meal with composition similar to the one employed in the present study. Mueller-Lissner and colleagues (Mueller-Lissner *et al*., 1982) showed similar data for a 5 mm OD, after administration of liquid meals, unlike the situation where more than one tubes are passing through the pylorus (Read *et al*., 1983) (Read *et al*., 1983). Therefore, the intestinal lumen of the tube employed in the present study should not interfere significantly with the physiological GI transfer process. A series of holes (55 - 65 cm proximal to the end of the tube) were used to access the antrum of the stomach and a further series of handmade holes (13.5 - 23.5 cm proximal to the end of the tube) proved to be adequate for aspirating (not without difficulties at often times) samples with increased viscosity from the upper small intestine, near the ligament of Treitz.

B.2.2.6. Study protocol

A schematic representation of the study protocol is given in Figure B.1.

Day -3:

Discontinue any medication and abstain from alcohol and smoking

Day -1:

20:00 - Stop eating (drink water ad libitum)

Experimental day:

8:00 - The volunteer arrives at the gastroenterology department of the Red Cross Hospital of Athens and is briefly examined to confirm his health status and compliance with the protocol.

8:30 - 9:00 - The volunteer is intubated with a naso-gastro-intestinal double lumen tube. Insertion of the tube was assisted by a guiding wire and its position was monitored fluoroscopically (fluoroscopic illustrations of the final tube position for each volunteer are given in Appendix II), to ensure that the administration and sampling area in the stomach is the antrum and the area from which the small intestine is sampled is the ligament of Treitz. After reaching its final position, the wire was removed and the subject laid semi-supine. Body posture may affect distribution of contents but does not seem to affect gastric emptying rates (Steingoetter *et al*., 2006). The stomach was emptied from mucus secretions induced in response to the tube insertion/positioning procedure, as confirmed by the pH values of two preliminary samples aspirated from the stomach and the upper intestine, respectively.

9:00 - Just before administration the meal is prepared. The ingredients were homogenized using a Multi Pyrex® food processor. 50 mL water containing 100 mg phenol red were added to the mixture. Phenol red is used as a non-absorbable water flux indicator, that allows for monitoring water-flux throughout the GI meal transit process (French *et al*., 1968; Wiggins and Dawson, 1961). The meal was administered via the gastric port of the tube to the antrum using 60 mL-capacity syringes within 15 - 20 minutes.

9:30 - The paracetamol and danazol solutions (Phase I) or suspensions (Phase II) were administered.

9:30 - 13:30 - Samples were aspirated from the stomach (at 15, 75, 135, 195 min after administration of the drugs, 15 mL per sample) and from the upper small intestine (at 30, 60, 90, 120, 150, 180, 210, 240 min after the administration of the drugs, 15 mL per sample) with the help 10-mL or 20-mL ca. syringes.

13:30 - 14:00 - The naso-gastro-intestinal tube was removed and after a brief examination by the doctor the volunteer was free to leave the hospital.

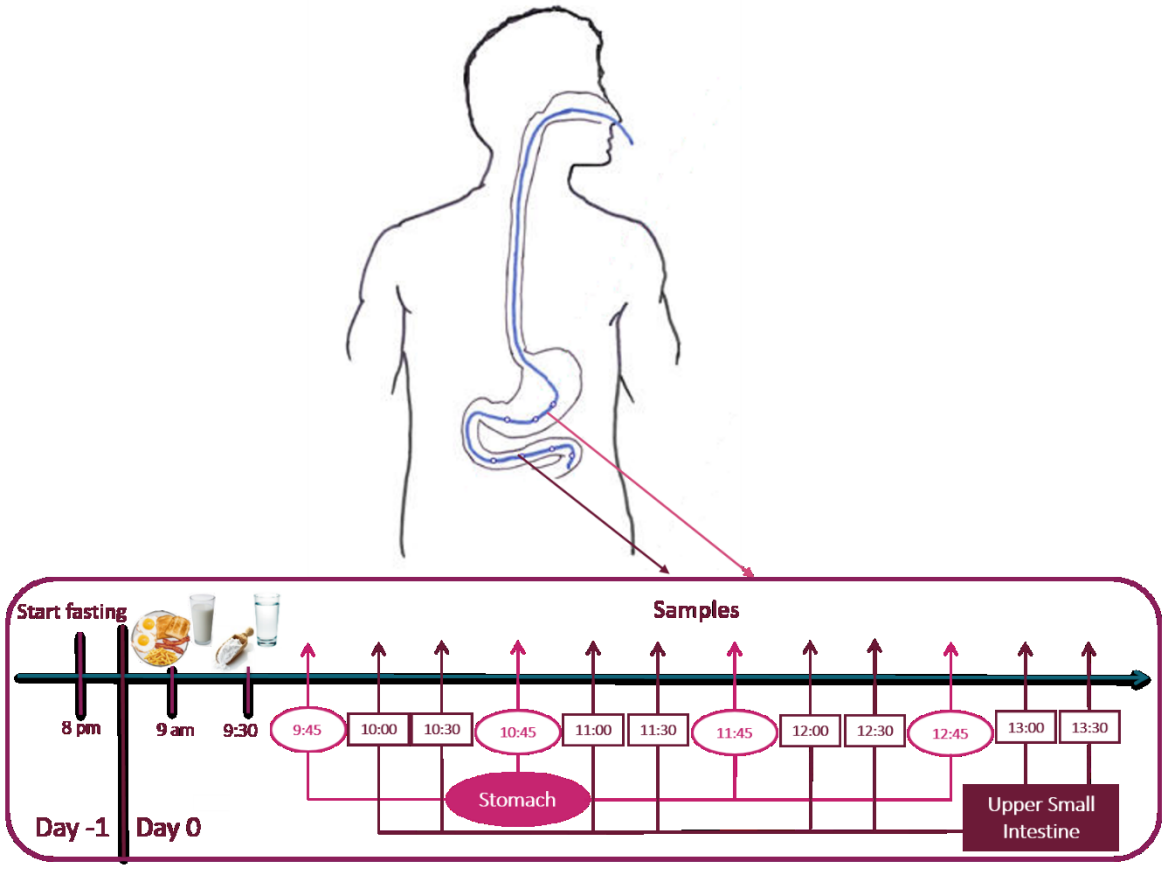

Figure B.1: Schematic representation of the clinical study protocol.

B.2.2.7. Sample treatment

Immediately upon aspiration, the volume, pH and buffer capacity of samples was measured. Six hundred microliters of the aspirated sample were transferred in six vials, 100 µL in each vial, for assaying the total content of phenol red, paracetamol, and danazol, in duplicate. A cocktail of lipase/protease inhibitors consisting of 50 mM diisopropylfluorophosphate, 50 mM diethyl(p-nitrophenyl)phosphate, 50 mM acetophenone, and 250 mM phenylboronic acid was added at 2% v/v to the remaining sample (Hernell *et al.*, 1990) which was then divided in two subsamples. The first was stored at -70°C for further analyses. The second was immediately centrifuged (11000 g, 37°C, 10 min) at the hospital to eliminate remaining solid API particles in the case of suspensions administration and subsequently ultracentrifuged (410174 g, 37°C, 2 h) to obtain the aqueous/micellar phase in which the concentrations of paracetamol and danazol were assayed. Two vials were prefilled with 100 µL of the aqueous phase for the analysis of paracetamol and two vials were prefilled with 200 µL for the analysis of danazol, each in duplicate. The remaining volume of the aqueous phase was stored at -70°C.

B.2.2.8. Analytical methods

All analytical methods are described in detail in Appendix III.

B.2.3. *In vitro* application: experiments with the TIM-1 gastrointestinal model

A schematic representation of the TIM-1 model is given in Figure B.2. The system consists of four serial compartments simulating the stomach, duodenum, jejunum and ileum. Each compartment consists of two connected equal basic units with a glass jacket and flexible walls inside. Mixing of the contents and temperature control is achieved by circulating water around the flexible walls. Peristaltic valve pumps connect the compartments and control the longitudinal transit of contents. The volume of contents is controlled by level sensors. A pre-set pH curve for each compartment is monitored with pH probes. pH is regulated with secretion of 1M hydrochloric acid (gastric compartment) or 1M sodium bicarbonate (intestinal compartments). Drug and digestion products are removed through filters applied to the jejunal and ileal compartments.

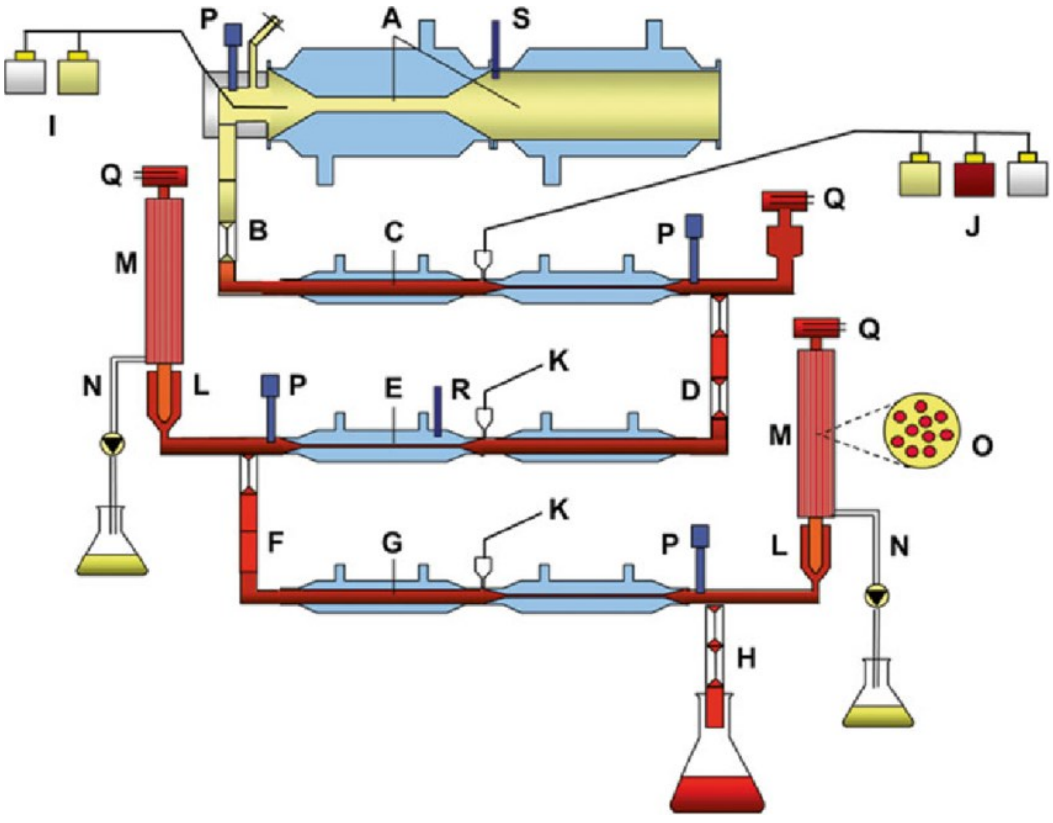

Figure B.2. Schematic representation of the TIM-1 model. (A. gastric compartment; B. pyloric sphincter; C. duodenal compartment; D. peristaltic valve; E. jejunal compartment; F. peristaltic valve; G. ileal compartment; H. ileocecal valve; I. gastric secretion; J. duodenal secretion; K. bicarbonate secretion; L. pre-filter; M. filtration system; N. filtrate with bio-accessible fraction; O. hollow fiber system (cross section); P. pH electrodes; Q. level sensors; R. temperature sensors; S. pressure sensor)

Prior to the performance of each experiment the secretions fluids (e.g. gastric juice with enzymes, electrolytes, porcine bile and pancreatic juice) were freshly prepared, the pH electrodes were calibrated, and filter units were installed.

Before introduction into the gastric compartment the high-fat, high-calorie meal was masticated with a food processor and mixed with artificial salivary fluid containing electrolytes and a-amylase. 150 g meal, 45 mL water (of which 15 mL phenol red 0.2% aqueous solution), 70 g GES, and 10 g gastric start residue (enzymes, HPMC 0.4% and bile 0.04% solution) were mixed and added to the gastric compartment at the beginning of the experiment. The amount of meal introduced in TIM-1 was about 30% of the meal administered to adults in fed state clinical studies. The total volume introduced in the gastric compartment was 300 mL.
The duodenal compartment was filled with 60 g of a solution consisting of 22.5 g SIES, 22.5 g pancreatin solution, 45 g bile solution and 2 mg trypsin in 1 mL SIES (duodenal start residue). The jejunal compartment was filled with a mixture of 35 g SIES, 35 g pancreatin solution and 70 g bile solution (jejunal start residue). The ileum compartment was filled with 140 g SIES.

As soon as the temperature in all compartments reached 37°C the drugs were administered in the gastric compartment. In line with the reduced volume of meal, the doses of paracetamol and danazol were scaled down by 30% compared to the human doses. To simulate the conditions applied in the clinical study, each experiment was designed to involve the administration of drug solutions or the administration of drug suspensions. In experiments with drug solutions, paracetamol solution was prepared by dissolving 150 mg in 18 mL tap water and danazol solution was prepared by dissolving 30 mg in 7 mL sunflower oil. In experiments with drug suspensions, paracetamol suspension was prepared by suspending 150 mg in 12.5 mL tap water and danazol suspension was prepared by suspending 30 mg in 12.5 mL water. All solutions and suspensions were prepared few minutes prior to administration. Each experiment was performed in duplicate. In Figure B.3. a picture of TIM-1 model while running the experiment is presented.

Experiments were performed at two different sites: at Pfizer, UK, and at the TIM Company, The Netherlands. Specifically:
- Two experiments with paracetamol solutions and two experiments with paracetamol suspensions were performed at Pfizer, UK. Due to national regulations in the UK, experiments with danazol were not performed at Pfizer.

- Two experiments with paracetamol and danazol solutions and two experiments with paracetamol and danazol suspensions were performed at the TIM Company, The Netherlands.

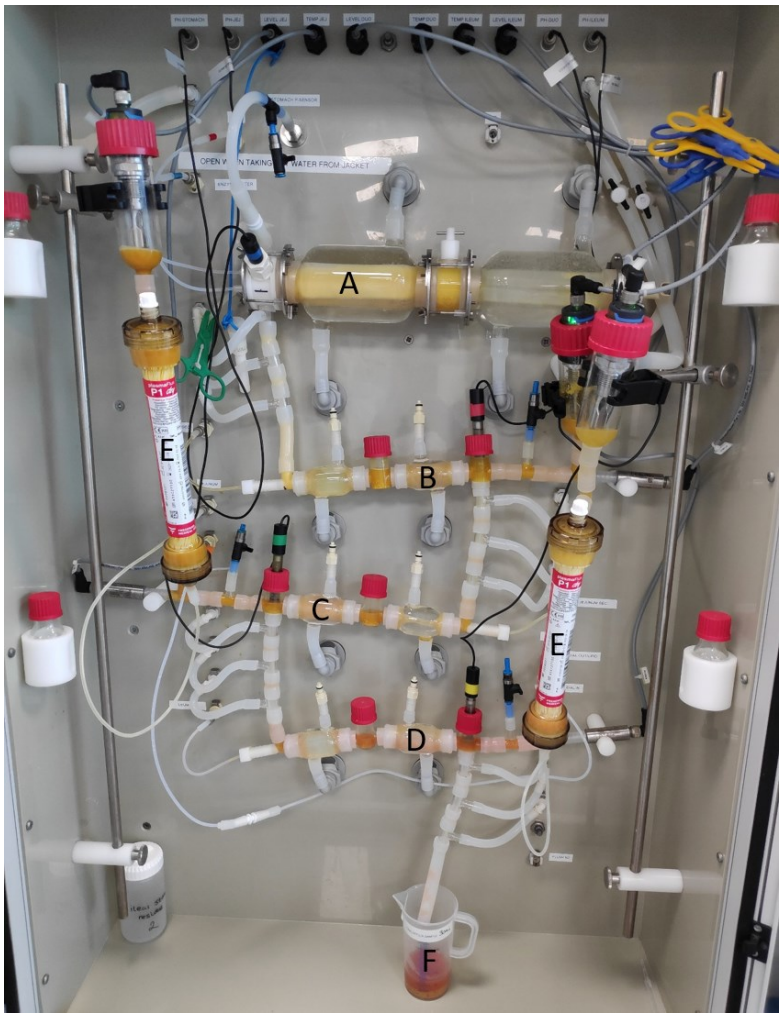

Figure B.3. Photograph of the TIM-1 model. A. gastric compartment; B. duodenal compartment; C. jejunal compartment; D. ileal compartment; E. filtration system; F. ileal efflux

In experiments performed at the TIM company, no phenol red was included in the meal. Samples from the gastric, duodenal, and jejunal compartments were collected at various time-points, as shown in Figure B.4. To simulate the housekeeper wave, at 180 min, the remaining contents of the gastric compartment were manually collected, mixed with 30 mL of the duodenal start residue, the pH was adjusted to the pH of the duodenal compartment with sodium bicarbonate, and the mixture was transferred into to the duodenal compartment. Therefore, the last sampling point from the gastric compartment was obtained at 180 min and not at 195 min as in the clinical study.

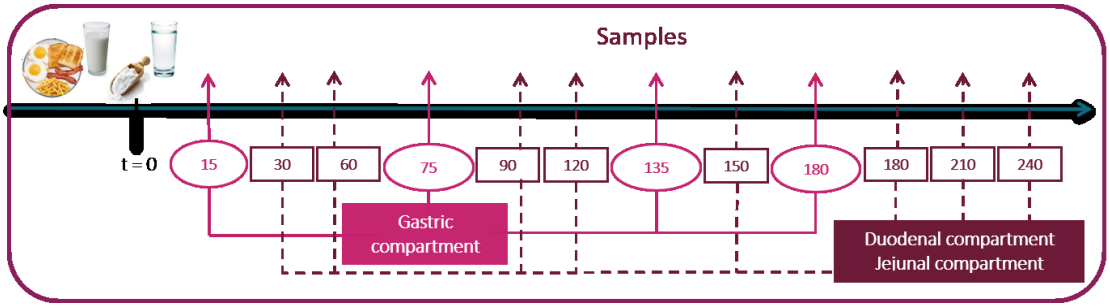

Figure B.4. Schematic representation of the TIM-1 sampling protocol from the contents of the gastric, duodenal and jejunal compartments.

At Pfizer, 3 mL samples were collected from the gastric compartment at all experiments. In two of the experiments (one solution and one suspension) 15 mL samples were collected from the duodenal compartment and 3 mL samples from the jejunal compartment. In the remaining two experiments (one solution and one suspension) 15 mL samples were collected from the jejunal compartment and 3 mL samples from the duodenal compartment. Collection of samples with larger volume from these compartments aimed at the micellar phase acquisition. Portions of those samples were immediately centrifuged (11000 g, 37 °C, 10 min) to eliminate solid particles and subsequently ultracentrifuged (410174 g, 37 °C, 2 h) to obtain the micellar phases. At the TIM Company, 1 mL samples were collected from the gastric, the duodenal and the jejunal compartments.

B.2.3.1 Sample Analysis

All samples were analyzed for their drug content. Based on data from the TIM Company, paracetamol average recovery (% of intake) was 98% for the solution experiments and 107% for the suspension experiments. Danazol average recovery (% of intake) was 84% for the solution experiments and 65% for the suspension experiments, indicating that a substantial amount of API is retained into the system.

At Pfizer, samples were additionally analyzed for their lipid content, micellar phases of duodenal and jejunal compartment samples were analyzed for their lipid content, samples from gastric and duodenal compartments were analyzed for their phenol red content (phenol red in the contents of jejunal compartment was not assayed as it is removed from this compartment through the filters and, therefore, cannot be used as water-flux indicator in this compartment), and finally samples of the porcine bile 100% solution, samples from duodenal and jejunal compartment, and their micellar phases were analyzed for their bile acid content.

Analytical methods for paracetamol, danazol, phenol red, lipid species, and bile acids were the same to those used for the human aspirates, listed in Appendix III.

B.2.4. Data treatment

In all cases:

- Time zero designates the time of drug administration with a glass of water, i.e. 30 min after initiation of meal consumption (adult data) and few minutes after introducing the meal in the gastric compartment (TIM-1 data).
- If the result of a specific measurement is <LOQ (data in Appendices), the result was considered as zero for the construction of a boxplot and the calculation of mean (SD) values

B.2.4.1. Clinical study data

With regards to paracetamol and danazol, data are presented as Box-Whisker plots showing the median value, the 10^{th}, 25^{th}, 75^{th}, and 90^{th} percentiles and the individual outlying data points. The number of individual data points used for the construction of a box is indicated on top of the box. Within each box, horizontal solid lines indicate median values and horizontal dotted lines indicate mean values.

With regards to the physicochemical parameters measured, since the meal was administered to each volunteer twice, at two different occasions, individual data were summarized as mean (SD) values in Tables or as Box-Whisker plots by employing up to sixteen individual data points.

Lined boxplots show total amount per volume of aspirated samples and empty boxplots show the respective apparent concentrations in the aqueous/micellar phase. Yellow boxplots represent data in the stomach whereas lime boxplots represent data in the upper small intestine.

B.2.4.2. TIM-1 data

In all graphs individual data are presented with lines. Data from both the duodenal and the jejunal compartment of TIM-1 are discussed versus the same set of data collected from the ligament of Treitz of adults.

C. RESULTS AND DISCUSSION

C.1. The standard meal

C.1.1. Physicochemical characteristics of the homogenized standard meal

The physicochemical characteristics of the meal administered to the volunteers are presented in Table C.1. Data are listed in Appendix IV. The values are generally in line with previously reported data characterizing the standard meal (Klein *et al*., 2004). Small deviations could be attributed to the inclusion of 50 mL aqueous phenol red solution in the test meal applied in this study (Pentafragka *et al*., 2020a).

Table C.1. Physicochemical characteristics of the standard meal (containing in addition 50 mL aqueous phenol red solution) after homogenization. Values are mean ± SD (n=3 meal preparations)

Mass (g)	543.1 ± 0.4
pH	6.16 ± 0.05
Buffer capacity (mmol/L/ΔpH) using 0.1N NaOH	26.8 ± 2.3
Osmolality (mOsm/kg)	438.0 ± 4.5
Surface tension (mN/m) of supernatant after ultracentrifugation	43.66 ± 0.86

C.1.2. The impact of homogenization on the texture of the standard meal

The particle size distribution of the meal particles on a volume basis and on % volume basis, after chewing and after homogenization, is given in Table C.2. Data are listed in Appendix V. On average, chewing of the meal led to salivary secretions of about 90 mL (622 mL vs. 532 mL). The % volume of particles larger than 2 mm was 15% higher than in the homogenized meal. The % volume of particles between 1 mm and 2 mm was similar in the homogenized and the chewed meal, and the % volume with particles smaller than 1 mm was 16% lower in the chewed meal.

The particle size distribution as % number of particles and as % cumulative number of particles, for particles smaller than 1 mm, is also presented in Figure C.1. Both the chewed and homogenized meal curves display maxima at the same particle sizes.

Table C.2: Particle size distribution on a volume basis (mean ± SD, n=3) and particle size distribution on % volume basis (mean, n=3) for the standard meal (containing in addition 50 mL aqueous phenol red solution) after chewing and after homogenization.

	Meal after chewing		**Meal after homogenization**	
	Volume (mL)	**% total**	**Volume (mL)**	**% total**
Total	622 ± 67	(100)	532.0 ± 1.6	(100)
> 2 mm	155 ± 33	25	52 ± 11	10
1 -2 mm	90 ± 18	14	70 ± 19	13
100 µm – 1mm	377 ± 26	21	411±19	38
10 µm – 100 µm		30		24
1 µm – 10 µm		7		13
< 1µm		3		2

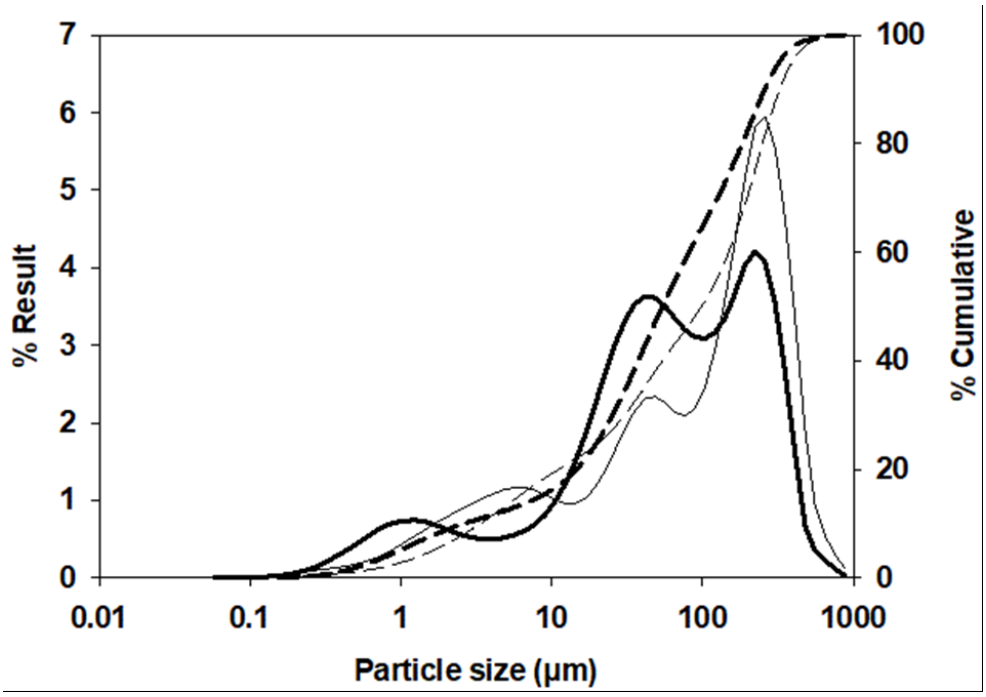

Figure C.1. Percent number of particles (continuous lines) and percent cumulative number of particles (dashed lines) vs. the size of particles with size up to 1 millimeter. Bold lines: chewed meal (n=3). Thin lines: homogenized meal administered to the volunteers (n=3).

Viscosity data of the chewed and homogenized meals at ascending shear rates of 50 s^{-1}, 100 s^{-1} and 200 s^{-1}, at 25°C and 37°C are presented in Table C.3. Data are listed in Appendix IV. Meal viscosity was in line with previously reported data for the viscosity of the standard meal (Pao *et al*., 1998). It decreased with increasing shear rates, indicating pseudo-plastic characteristics. For a given temperature and shear rate, viscosity of the chewed meal was slightly higher and more variable than the homogenized meal's. Apparently, salivary secretions counterbalance the higher percentage of bigger particles in the chewed vs. the homogenized meal, resulting in similar viscosities.

Table C.3. Viscosity (mean ± SD, n=3) of the standard meal (containing in addition 50 mL aqueous phenol red solution) at 25 °C and at 37 °C, after chewing and after homogenization.

	Meal after chewing		**Meal after homogenization**	
Shear rate (s^{-1})	**25 °C**	**37 °C**	**25 °C**	**37 °C**
50	1894 ± 1300	1862 ± 861	1731 ± 225	1729 ± 80
100	1724 ± 794	1648 ± 594	1605 ± 228	1582 ± 166
200	1000 ± 287	877 ± 197	945 ± 107	938 ± 65

Normally when eating, food is stacking up in the stomach and layer by layer the gastric contents become pasty and then liquid as they approach the pylorus (Schulze, 2006). Based on MRI images, heterogeneity of gastric contents is decreasing 30 min after initiation of meal consumption (Koziolek *et al*., 2014b). Thus, considering the meal's particle size and viscosity findings, 30 min after administration of the homogenized meal, deviations from the actual conditions at 30 min after chewing and swallowing the meal are expected to be minimal.

C.2. Disposition of highly permeable drugs in the upper GI lumen after the standard meal

C.2.1. Water flux estimated through phenol red data

Total phenol red amounts per volume of aspirated contents are presented in Figure C.2. (Pentafragka *et al*., 2020a). Data are listed in Appendix VI.

Taking into account the volume of the meal containing the phenol red solution (~532 mL), the resting gastric volume (~30 mL) and the glass of water co-administered with the drugs (~200 mL), if no water flux had occurred in stomach during the residence of the meal the total phenol red amount per volume of gastric contents should have been ~130 μg/mL. However, mean values were much lower, indicating substantial secretions due to the hyperosmotic nature of

the meal, and practically no major changes in the bulk intragastric volumes. Similar observations have been previously made after administration of similar meals (Koziolek *et al.*, 2014b; Malagelada *et al.*, 1976).

In the upper small intestine total phenol red amounts per volume of contents are slightly lower than those in the stomach, indicating additional secretions occurring in the duodenum.

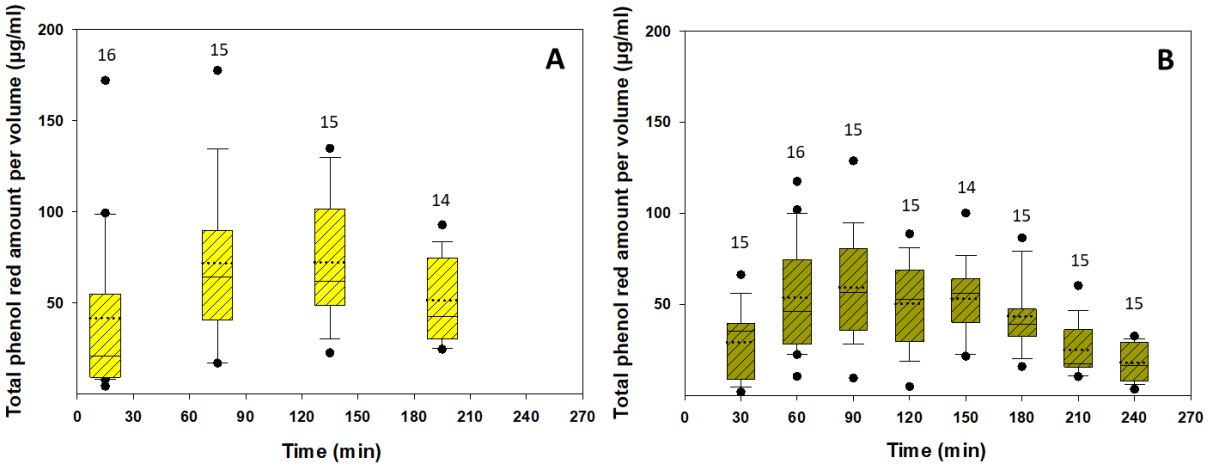

Figure C.2. Total phenol red amount per volume of antral contents (A) and contents of the upper small intestine (B).

C.2.2. Paracetamol in the upper GI lumen after administration in the antrum

Paracetamol data are presented in Figure C.3. (Pentafragka *et al.*, 2020a). Data are listed in Appendix VI.

C.2.2.1. Aqueous solution

Total paracetamol amounts per volume of contents decreased exponentially in the stomach (Figure C.3.A) and the upper small intestine (Figure C.3.B). As expected for a highly soluble drug, mean apparent concentrations in the aqueous phase of gastric contents were almost superimposable to the mean total amounts per volume of gastric contents (Figure C.3.A). Similar observations were made for the data in upper small intestine (Figure C.3.B). Apparent concentrations in the micellar phase of contents of the upper small intestine were lower than concentrations in the aqueous contents of gastric contents.

C.2.2.2. Aqueous suspension

Total amounts per volume decreased exponentially in the stomach (Figure 3C) and the upper small intestine (Figure C.3.D), and inter-subject variability was lower compared to the aqueous solution. Mean apparent concentrations in the aqueous phase of contents in stomach and in the micellar phase of contents in the upper small intestine were almost superimposable to the

corresponding mean total amounts per volume (Figures C.3.C and C.3.D), reflecting the high solubility characteristics of paracetamol. Apparent concentrations in micellar phase of contents of upper small intestine were lower than in the aqueous gastric contents.

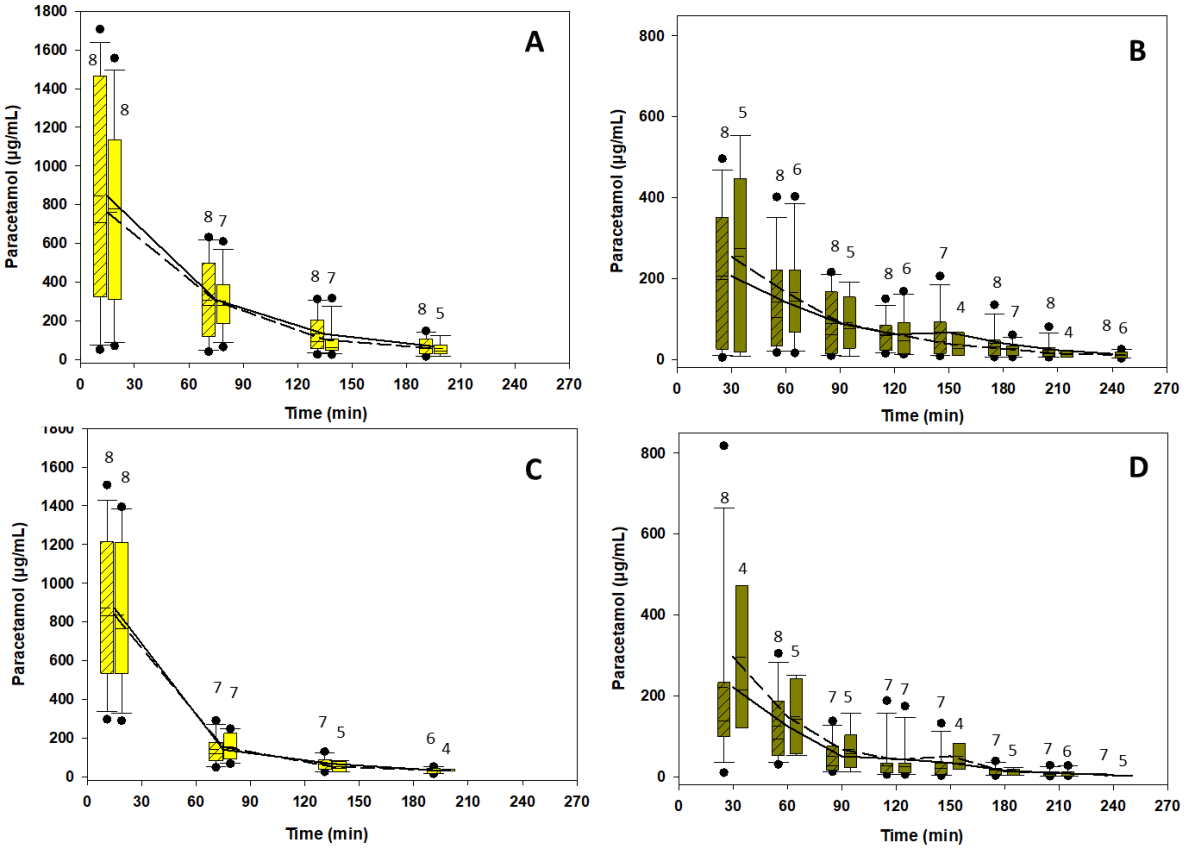

Figure C.3. Paracetamol in antral contents and contents of the upper small intestine after administration of aqueous solution (A and B, respectively) and aqueous suspension (C and D, respectively) in the antrum. Lined boxplots show total amount per volume of aspirated sample and empty boxplots show the respective apparent concentration in the aqueous/micellar phase. Continuous line shows the mean total amount per volume and dashed line shows the mean apparent concentration in the aqueous/micellar phase.

C.2.3. Paracetamol GI transfer after the standard meal

Individual total paracetamol amount per volume of intestinal contents vs. time data were considered for estimating GI transfer parameters, as previously done for similar data collected in the fasted state (Kourentas *et al.*, 2016a). The lack of data at times earlier than 30 min (Figures C.3.B and C.3.D), however, did not allow for successful fitting of the bi-exponential first-order model to the data. Phenol red data suggested practically unchanged volume of gastric contents (Figure C.2.A). Also. previous data support that gastric secretions in response to a similar meal follow apparent zero-order kinetics (Fordtran and Walsh, 1973). Finally, it has been shown that when the volume of a drug solution in a beaker is maintained constant and

there is simultaneous constant inflow of solution not containing the drug and constant outflow of the drug solution from the beaker, the drug concentration in the beaker over time reflects the first order emptying process of the drug from the beaker (Rowe and Morozowich, 1969).

Based on the above and given that total paracetamol amounts per volume of gastric contents decreased continuously with time, it was assumed that the gastric profiles reflect in essence the paracetamol gastric emptying process. Individual total drug amount per volume of contents vs. time data in stomach and in the upper small intestine were modelled by simultaneously fitting the following two equations to the data using Phoenix WinNonlin 8.2 (Certara USA, Inc., Princeton, USA):

$$f(t) = \frac{Dose}{V_G} \cdot e^{-k_G \cdot t} \quad (1)$$

$$f(t) = \frac{Dose}{V_I} \cdot \frac{k_G}{(k_G - k_I)} \cdot (e^{-k_I \cdot t} - e^{-k_G \cdot t}) \quad (2)$$

where k_G is the apparent first order gastric emptying rate constant, V_G is the apparent volume of gastric contents, k_I is the apparent duodenal elimination rate constant, and V_I is the apparent volume of duodenal contents. Since data after the administration of solution and suspension are similar for total amounts per volume and concentrations in stomach ($p>0.05$, paired t-test or Wilcoxon test depending on data normality), individual data were considered simultaneously. Individual data sets showed continuously decreasing pattern in stomach and in upper small intestine and individual total amounts per volume as well as the best fitted lines are presented in Figure C.4.

The values of estimated parameters are presented in Table C.4. The validity of the modelling approach was additionally confirmed by estimating the rate constant for the terminal phase of the data in upper small intestine. If gastric emptying is assumed to be much slower than the elimination from upper small intestine (Table C.4), the terminal phase of the data in upper small intestine should practically reflect the input process in the small intestine, i.e. the gastric emptying process [flip-flop kinetics (Shargel and Yu, 1999)]. Indeed, the rate constant estimated from the terminal phase of the data in the small intestine was 0.018 (0.002) min^{-1} i.e. identical to the estimated k_G value in Table C.4. The estimated half-life for paracetamol gastric emptying was 38.5 min, more than two times longer than the estimated half-life for drug gastric emptying after administration of an aqueous drug solution in the fasted state (Kourentas *et al*., 2016a). Estimated apparent volume of gastric contents 30 min post meal administration (451 mL) is in line with previous studies indicating that the intragastric volumes are similar to meal volumes at this time point (Koziolek *et al*., 2014b; Malagelada *et al*., 1976).

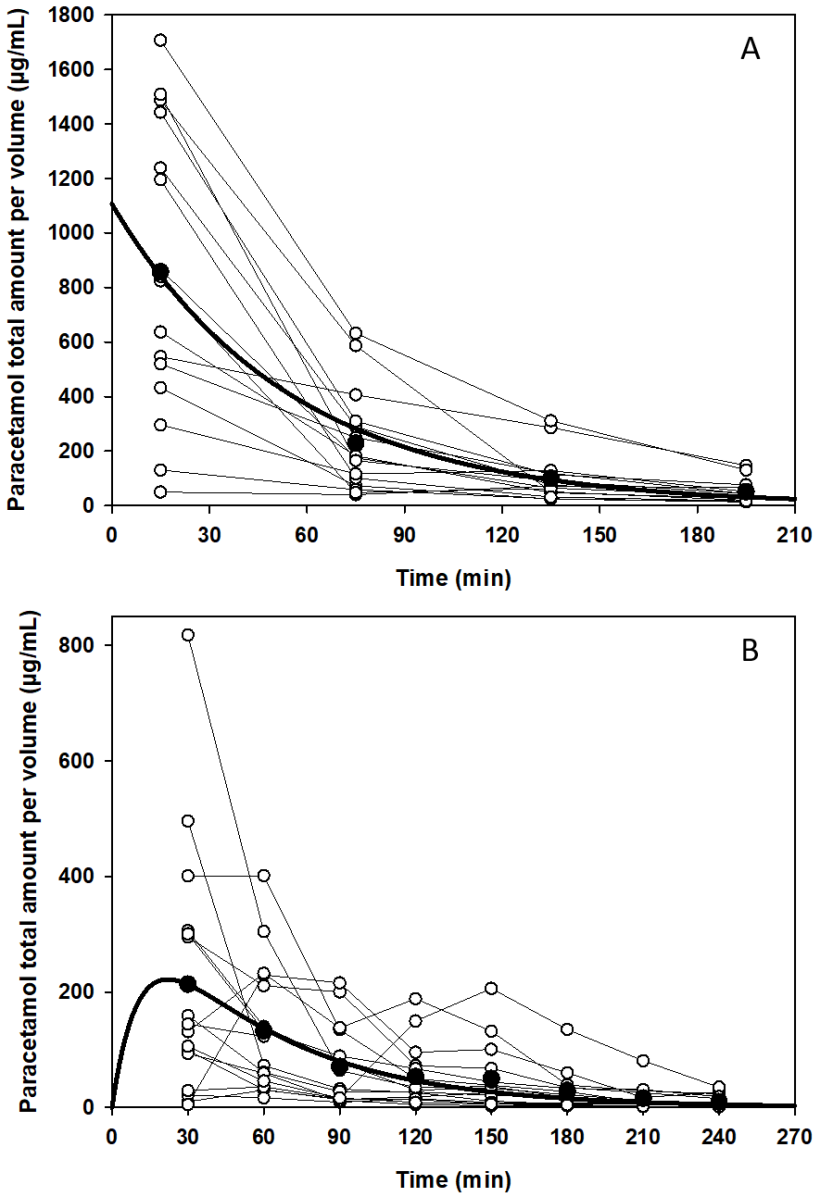

Figure C.4. Individual profiles for total paracetamol amounts per volume (µg/mL) in antral contents (A, n=60) and contents of the upper small intestine (B, n=121) after administration of aqueous solution or aqueous suspension in the antrum. Black circles are mean data; bold lines are the best fitted lines after simultaneous fitting of equations 1 and 2 to individual data. Estimated parameters and measures of fit are presented in Table C.4.

Table C.4. Estimated apparent gastric emptying rate constant of paracetamol, k_G, apparent volume of gastric contents, V_G, apparent rate constant for paracetamol elimination from the upper small intestine, k_I, and apparent volume of contents in the upper small intestine, V_I, for paracetamol administered 30 minutes after the standard meal, based on the results of the simultaneous fitting of equation 1 and equation 2 to the individual total paracetamol amounts per volume of antral contents and contents of the upper small intestine. Standard error of estimation in parentheses; n=60 individual time points for the fitting of equation 1 and n= 121 individual time points for the fitting of equation 2; $R^2 = 0.6$ ($p < 0.0001$)

k_G (min^{-1})	0.018 (0.003)
V_G (mL)	451 (50)
k_I (min^{-1})	0.091 (0.075)
V_I (mL)	301 (268)

C.2.4. Danazol in the upper GI lumen after administration

Danazol data are presented in Figure C.3. (Pentafragka *et al*., 2020a). Data are listed in Appendix VI.

C.2.4.1. Sunflower oil solution

Total danazol amounts per volume of gastric and upper small intestinal contents were highly variable. High variability of upper small intestinal danazol data has been previously observed after administration of an olive oil danazol solution with a liquid meal too (Vertzoni *et al*., 2012).

Apparent concentrations in the aqueous phase of gastric contents were lower than total amounts per volume, ranging from 0.1 to 1.6 μg/mL i.e. close to solubility of danazol in water ≈ 1μg/mL (Sunesen *et al*., 2005). Apparent concentrations in the micellar phase of contents of upper small intestine ranged from 0.04 to 32 μg/mL i.e. only slightly lower than danazol solubility in the micellar phase of intestinal aspirates measured previously: 40±43μg/mL, n=44, 37°C (Vertzoni *et al*., 2012). Contrary to paracetamol, apparent danazol concentrations in the micellar phase of contents in the upper small intestine were higher than in the aqueous phase of gastric contents, reflecting the efficient transfer of lipophilic danazol from the long chain triglyceride solution into the bile salt micelles so that apparent concentrations are maintained close to saturation. It should be noted that, based on danazol solubility in the total and micellar contents of upper small intestine in the fed state, precipitation due to lipid digestion in the upper small intestine is unlikely.

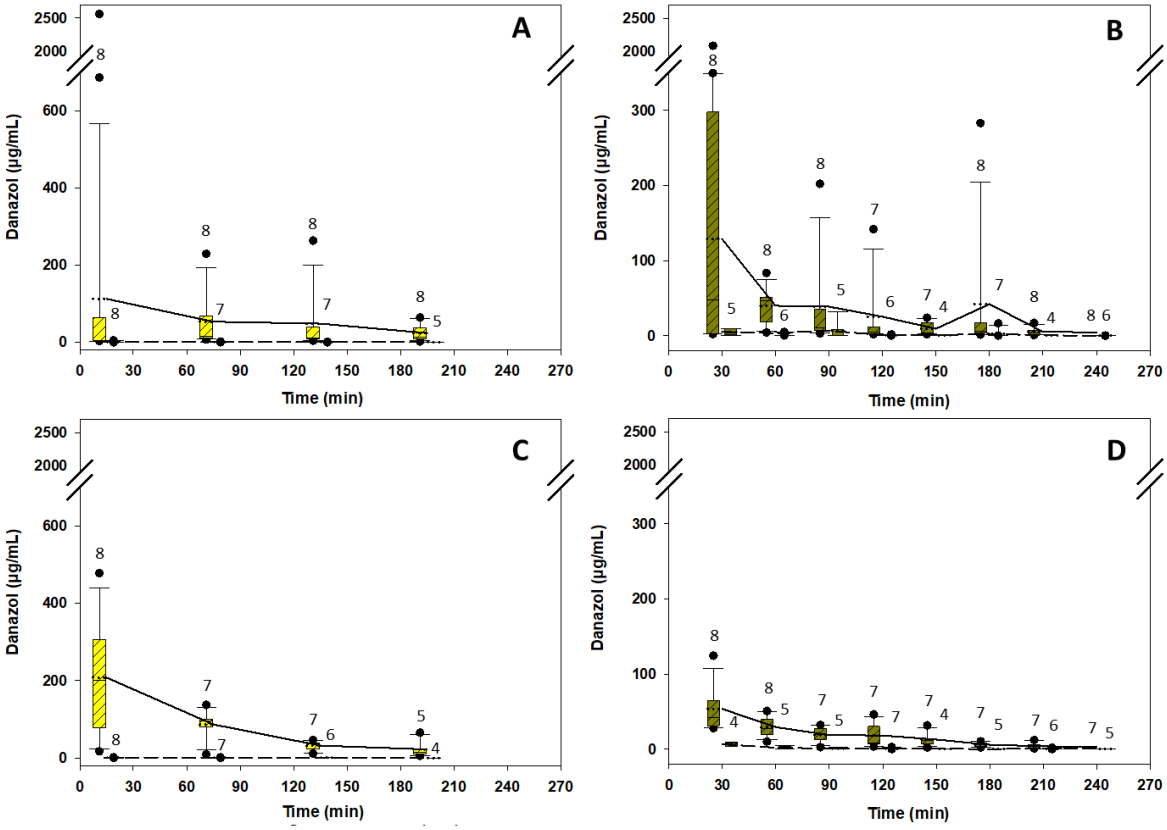

Figure C.5: Danazol in antral contents and contents of the upper small intestine after administration of sunflower oil solution (A and B, respectively) and aqueous suspension (C and D, respectively) in the antrum. Lined boxplots show total amount per volume of aspirated sample and empty boxplots show the respective apparent concentration in the aqueous/micellar phase. Continuous line shows the mean total amount per volume values and dashed line shows the mean apparent concentration in the aqueous/micellar phase.

C.2.4.2. Aqueous suspension

Inter-subject variability was lower compared to the solution administration. As with paracetamol, total amounts per volume decreased exponentially in the stomach and in the upper small intestine. Apparent concentrations in the aqueous phase of antral contents were very low, ranging from 0.2 to 1.7 µg/mL (solubility in water ≈ 1 µg/mL (Sunesen *et al.*, 2005). In the upper small intestine, apparent concentrations in the micellar phase ranged from 0.03 to 9 µg/mL, i.e. they are much lower than the apparent solubility in the micellar phase of intestinal aspirates, 40±43µg/mL (n=44, 37°C, Vertzoni *et al.*, 2012) and much lower than apparent concentrations after the sunflower oil solution, emphasizing the slower transfer of lipophilic danazol from solid particles rather than from the sunflower solution to the micellar phase.

C.2.5. Danazol GI transfer after the standard meal

Danazol sunflower oil solution data could not be modelled because of the high variability. A simultaneous fitting of equations 1 and 2 to the total amounts per volume of contents of the danazol suspension data was performed but the standard errors of estimates for k_I and V_I were very high. Thus, only the gastric emptying process after administration of the aqueous suspension could be describing by fitting equation 1 to the total amounts per volume of gastric contents. Individual data decreased continuously with time and together with the best fitted line, they are presented in Figure C.6.

Estimated values for k_G and V_G were 0.0145 (0.0046) min^{-1} and 386.9 (68.0) mL, respectively. The estimated half-life for gastric emptying is 47.8 min, somewhat longer than that estimated for paracetamol. It has been reported that hydrophobic solid drug particles administered in an aqueous suspension form in the antrum in the fasted state tend to agglomerate in the gastric contents and/or adhere on the gastric mucosa resulting to delayed gastric emptying rates (Kourentas *et al.*, 2016b). A similar phenomenon could be assumed for the fed state too. Estimated apparent volume of gastric contents, V_G, was lower than the one estimated after the paracetamol potentially reflecting differences between paracetamol and danazol particles distribution in stomach.

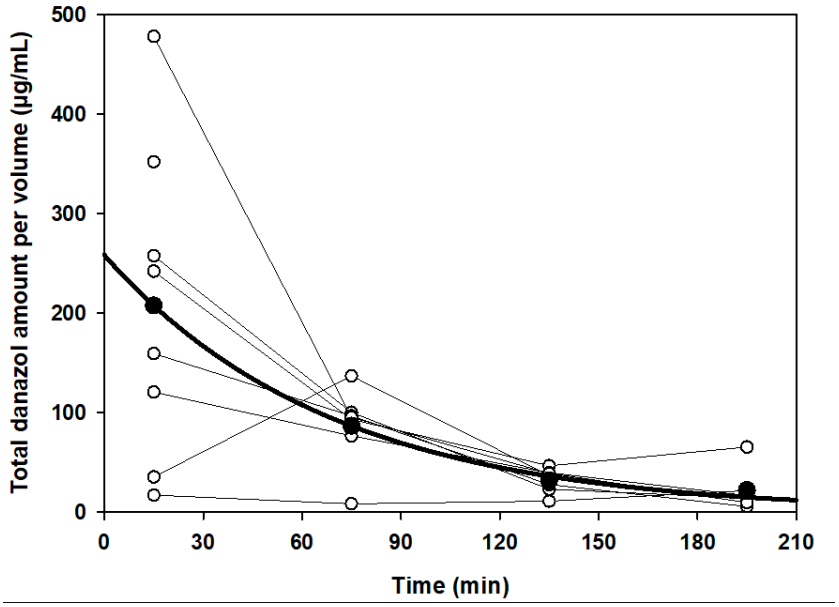

Figure C.6: Individual profiles for total danazol amounts per volume (µg/mL) in antral contents (n=28) after administration of aqueous suspension in the antrum. Black circles are mean data; bold line is the best fitted line to individual data (R^2 = 0.5; p <0.0001).

C.3. Physicochemical characteristics of contents in the upper GI lumen after the standard meal

C.3.1. Antrum

C.3.1.1. Characteristics of the total aspirated contents

pH and buffer capacity

pH and buffer capacity data of antral contents are presented in Figure C.7. (Pentafragka *et al*., 2020b). Individual data (Appendix VII) show low intra-subject variability for these two parameters after administration of the homogenized standard meal.

The median pH values at 15, 75, 15 and 195 min were 2.9, 3.1, 2.9, and 1.9, similar to previously reported data after the standard meal (Dressman *et al*., 1990; Koziolek *et al*., 2015; Rubbens *et al*., 2019). Previous studies have also shown that the pH of gastric contents is not affected significantly by prior homogenization of a solid meal (Malagelada *et al*., 1979; Figure A.1).

Mean buffer capacity of antral contents remained steady at approximately 20 mmol/mL/ΔpH during the 4 hours after meal administration. Previously reported buffer capacity data after administration of a homogenized liquid meal were similar to the data in this study (Kalantzi *et al*., 2006a, Table A.3.1.1).

Lipid species

Mean ± SD concentrations of lipid species in gastric aspirates over time are summarized in Table C.5. (Pentafragka *et al*., 2020b). High inter-subject and intra-subject variability is observed (Appendix VIII). Based on mean values, TGs, DGs, FAs and PC were comparatively the most abundant species, in line with previous data suggesting that intragastric lipolysis of TGs mainly generates DGs and FAs (Amara *et al*., 2019).

Only data after administration of a heterogeneous liquid meal were available to date (Armand *et al*., 1996) (Table A.3.1.1). Reported levels were much higher than those observed in this study, however, a direct comparison is not attempted because in addition to differences in composition, differences in meal texture can also affect concentrations of lipid species in the stomach. For example, gastric lipase output is higher after administration of liquid meals (Amara *et al*., 2019; Koziolek *et al*., 2018). It has also been shown that TGs in an emulsified meal are more accessible to lipase than in a minced solid meal, such that intragastric TG lipolysis is approximately 25% and 10%, respectively (Carrière *et al*., 2001).

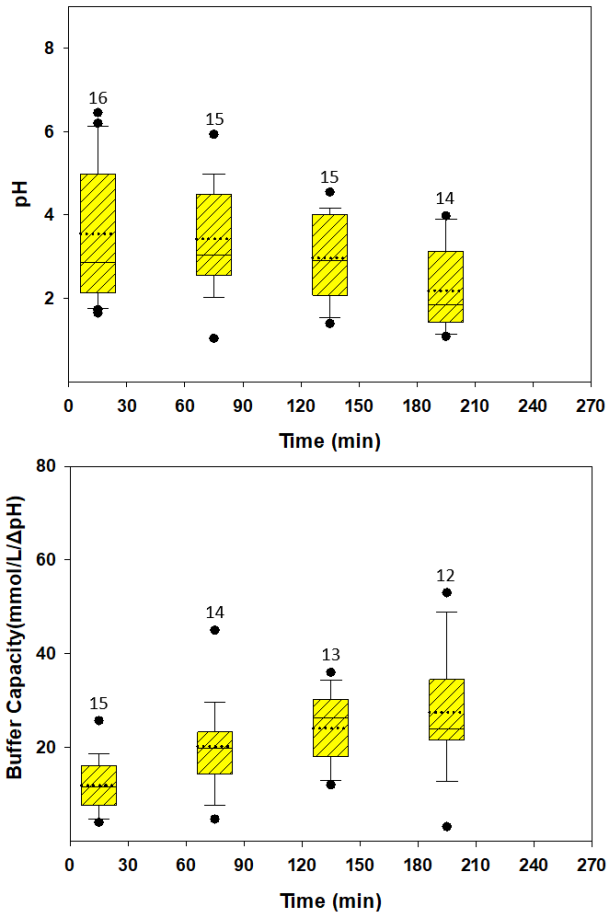

Figure C.7: pH and buffer capacity in antral contents after the standard meal.

Table C.5. Mean ± SD (n = 12-16) concentrations of lipid species in antral contents.

Time (min)	15	75	135	195
TGs (mM)	3.0 ± 3.7	2.7 ± 2.2	2.8 ± 1.8	2.2 ± 1.3
DGs (mM)	2.7 ± 2.8	4.1 ± 3.0	3.5 ± 2.3	2.6 ± 1.9
MGs (mM)	0.27 ± 0.31	0.44 ± 0.36	0.42 ± 0.38	0.26 ± 0.18
FAs (mM)	2.84 ± 3.08	4.0 ± 2.4	3.8 ± 2.5	3.1 ± 2.2
PC (mM)	3.45 ± 3.05	5.78 ± 3.05	5.5 ± 2.3	3.9 ± 1.6
lyso-PC (mM)	0.053 ± 0.065	0.11 ± 0.11	0.15 ± 0.17	0.13 ± 0.16
CHO (mM)	1.4 ± 1.4	2.0 ± 1.4	2.1 ± 1.4	1.3 ± 1.0

Viscosity

Gastric contents' viscosity is highly variable (Appendix VII, Figure C.6) (Pentafragka *et al*., 2020b). Pseudoplastic behavior is observed, with higher viscosity at lower shear rates. Mean values in the stomach at 100 s-1 are lower than the viscosity values of the homogenized meal (Table C.3) but they are 80-800 times higher than the viscosity values of gastric contents in the fasted state i.e. 1.4-6.4 mPa·s at 100 s-1 (Pedersen *et al*., 2013).

C.3.1.1. Characterisstics of the aqueous phase

Osmolality data and concentrations of lipid species revealed high inter-subject variability and high intra-subject variability (Appendices VII, VIII). Mean ± SD data for the aqueous phase of antral contents are summarized in Table C.6 (Pentafragka *et al*., 2020b).

Osmolality

Osmolality of the aqueous phase of intragastric contents was reduced compared to the osmolality of the aqueous phase of the standard meal (Table C.1), suggesting significant amounts of gastric secretions in response to the administration of the hyperosmotic standard meal. Higher osmolality was reported after a homogenous liquid meal (Kalantzi *et al*., 2006a) (Table A.3.1.1). Prior homogenization of a solid meal is reported to not affect intragastric osmolality values (Malagelada *et al*., 1979), so the difference is attributed to differences in meal texture and composition.

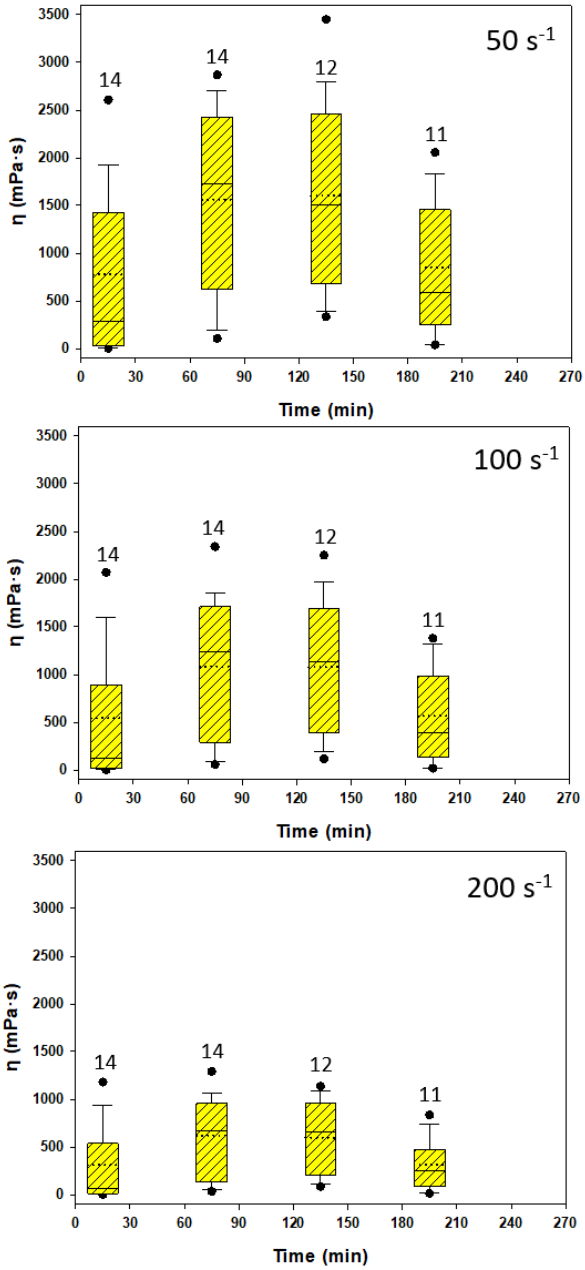

Figure C.8: Viscosity (37 °C) of antral contents after the standard meal.

Lipid species

Concentrations of lipid species in the aqueous phase were at least ten times lower than in the total aspirated samples (Table C.6 vs. Table C.5). FAs and PC were the most abundant lipid species, as in total aspirates.

Table C.6: Mean ± SD (n = 10-15) values for osmolality and concentrations of lipid species in the aqueous phase of antral contents.

Time (min)	15	75	135	195
Osmolality (mOsm/kg)	153 ± 126	259 ± 112	304 ± 109	260 ± 61
TGs (mM)	< 0.001	< 0.001	< 0.001	< 0.001
DGs (mM)	0.027 ± 0.041	0.038 ± 0.045	0.037 ± 0.037	0.012 ± 0.013
MGs (mM)	0.029 ± 0.064	0.027 ± 0.027	0.036 ± 0.024	0.016 ± 0.014
FAs (mM)	0.215 ± 0.339	0.246 ± 0.234	0.309 ± 0.190	0.112 ± 0.072
PC (mM)	0.51 ± 0.93	0.65 ± 0.69	0.77 ± 0.58	0.23 ± 0.20
lyso-PC (mM)	0.009 ± 0.024	0.0057 ± 0.0077	0.010 ± 0.011	0.009 ± 0.010
CHO (mM)	0.067 ± 0.065	0.13 ± 0.13	0.125 ± 0.094	0.051 ± 0.044

C.3.1. Upper small intestine

C.3.1.1. Characteristics of the total aspirated contents

pH and buffer capacity

pH and buffer capacity data of contents of the upper small intestine are presented in Figure C.9 (Pentafragka *et al*., 2020b). Individual data (Appendix VII) suggest low intra-subject variability for the pH, and for buffer capacity, somewhat higher variability than in the antrum.

Median pH values at 30, 60, 90, 120, 150, 180, 210 and 240 min were pH 6.3, 5.8, 5.4, 5.2, 5.1, 5.0, 5.6 and 4.9, respectively (Figure C.9). The extended meal effect on the pH of contents in the upper small intestine is in line with previous data suggesting that gastric emptying of the standard meal lasts more than 4 hours. The overall median value estimated was pH 5.3, lower than the overall median pH 6.3 reported previously after administration of another standard meal example (Dressman *et al*., 1990) but similar to the median pH 5.4 for 30-240 min after administration of the standard meal and the weak acid diclofenac, reported by (Rubbens *et al*., 2019). It could be assumed that the high buffer capacity of contents in the upper small intestine after the standard meal may eliminate potential effects of co-administered acidic drugs on luminal pH, in contrast to the fasted state (Litou *et al*., 2020). Previous data show that the pH of duodenal contents is not affected significantly by homogenization of a solid meal (Malagelada *et al*., 1979).

Mean buffer capacity decreased from 27.6 mmol/L/ΔpH at 30 min to 15.5 mmol/L/ΔpH at 240 min and is generally in line with previously published data after administration of liquid meals (Kalantzi *et al*., 2006a; Vertzoni *et al*., 2012) (Table A.3.2.1).

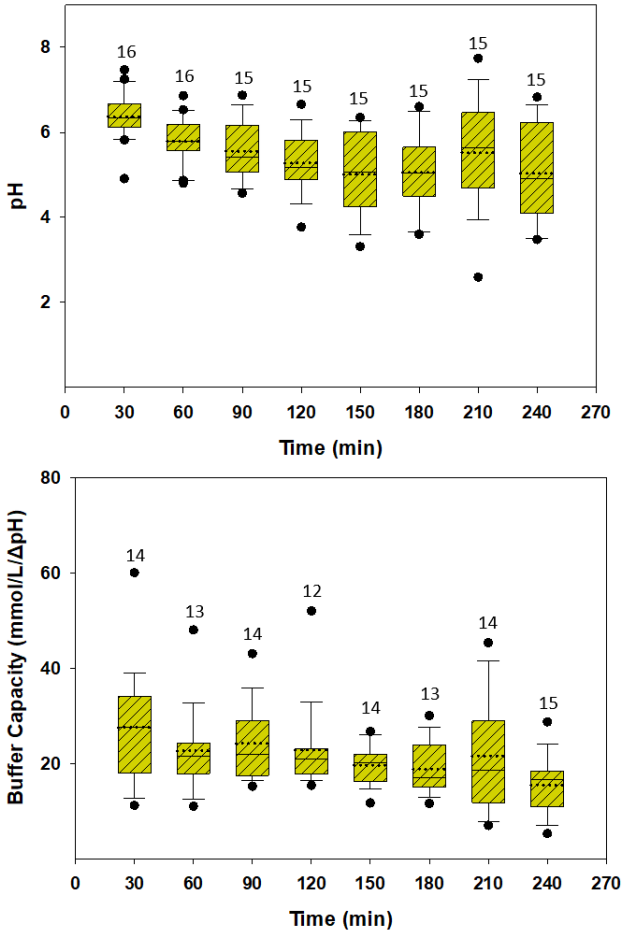

Figure C.9: pH and buffer capacity in contents of the upper small intestine after the standard meal.

Lipid species and Bile acids

Concentrations of lipid species and bile acids (Appendix VIII) revealed high inter-subject and high intra-subject variability. Mean ± SD values are summarized in Table C.7 (Pentafragka *et al.*, 2020b).

In line with data for the antrum, FAs and PC were comparatively the most abundant lipid species. However, mean FAs concentrations were much higher in the upper small intestine (Table C.7 vs. Table C.5). Differences from previously reported data cannot be evaluated, since they are available only after administration of liquid meals (Armand *et al.*, 1996; Hernell *et al.*, 1990; Kalantzi *et al.*, 2006b; Vertzoni *et al.*, 2012) (Table C.3.2.1) and differences in meal composition and texture matter for lipid digestion. For example, pancreatic lipase secretion is higher after a liquid meal than after a solid-liquid meal with the same fat amount, and thus, duodenal lipolysis rates are lower when solid-liquid meals are ingested (Amara *et al.*, 2019; Carrière *et al.*, 2001).

The predominant bile acids were glycoconjugates and the relative mean luminal concentrations were GCDC > GC > GDC > TC ~ TCDC > UDC (Table C.7.). Mean total bile acid content peaked at 30 min to 13.1 mM and then gradually decreased. Previous data obtained after liquid meals (Armand *et al*., 1996; Hernell *et al*., 1990; Kalantzi *et al*., 2006a; Vertzoni *et al*., 2012) are generally in line with data of this study, since meal texture does not affect bile acid output (Malagelada *et al*., 1979).

Viscosity

Aspirated samples showed pseudoplastic behavior and data were highly variable (Appendix VII, Figure C.10) (Pentafragka *et al*., 2020b). To date, only the kinematic viscosity in the fasted upper small intestine has been reported (Litou *et al*., 2016). Assuming that the density of contents in the upper small intestine in the fasted state is slightly higher than that of water, viscosity in the fasted state is estimated to be slightly higher than 1 mPa·s, i.e. much lower than in the fed state as measured in this study (e.g. 103-516 mPa·s at 100s-1).

C.3.1.1. Characteristics of the micellar phase

Osmolality

Osmolality data are summarized in Table C.8 (Pentafragka *et al*., 2020b). Previous data after liquid meals (Table A.3) are in line with data in this study.

Lipid species and bile acids

Lipid species and bile acids concentrations indicated high inter-subject and high intra-subject variability (Appendix VIII). Mean (SD) values are summarized in Table C.8. Major lipid species in the micellar phase are FAs and lyso-PC.

With regards to bile acids, at 30 min, most of the total bile acids are present in the micellar phase of contents but, at later times, the bile acid content in the micellar phase is reduced (Table C.8 vs. Table C.7). Potential reasons for this phenomenon include the association of bile acids in intermediate colloidal structures during the course of lipid digestion (Sadeghpour *et al*., 2018) and the adsorption of bile acids onto residues of standard meal contents (Rubbens *et al*., 2019).

Table C.7: Mean ± SD (n = 10-15) concentrations of lipid species and bile acids in contents of the upper small intestine after the standard meal.

Time (min)	30	60	90	120	150	180	210	240
TGs (mM)	1.5 ± 2.0	1.4 ± 1.2	1.9 ± 2.7	3.1 ± 5.5	1.01 ± 0.95	1.5 ± 2.8	0.24 ± 0.32	0.18 ± 0.21
DGs (mM)	3.4 ± 4.6	2.4 ± 1.9	2.3 ± 1.5	2.2 ± 1.0	1.7 ± 1.0	1.5 ± 1.3	0.56 ± 0.76	0.48 ± 0.51
MGs (mM)	1.13 ± 0.59	1.02 ± 0.62	0.92 ± 0.52	0.80 ± 0.46	0.65 ± 0.23	0.5 ± 0.3	0.27 ± 0.19	0.27 ± 0.16
FAs (mM)	21.3 ± 9.6	18.2 ± 8.5	16.4 ± 5.4	15.9 ± 4.7	13.8 ± 6.1	11.8 ± 6.4	6.3 ± 2.6	5.2 ± 3.6
egg-PC (mM)	4.2 ± 5.0	4.7 ± 3.1	4.6 ± 3.0	4.1 ± 2.2	3.6 ± 2.3	3.5 ± 4.7	1.0 ± 1.1	0.98 ± 0.99
lyso-PC (mM)	2.6 ± 1.4	2.6 ± 1.3	1.8 ± 0.9	2.0 ± 1.1	1.53 ± 0.89	1.5 ± 1.0	1.20 ± 0.63	0.78 ± 0.63
CHO (mM)	3.3 ± 3.0	2.7 ± 1.4	2.1 ± 1.2	2.0 ± 1.1	1.72 ± 0.86	1.30 ± 0.76	0.74 ± 0.54	0.66 ± 0.43
TC (mM)	1.52 ± 0.99	1.19 ± 0.76	0.93 ± 0.50	0.65 ± 0.59	0.83 ± 0.47	0.71 ± 0.54	0.64 ± 0.49	0.46 ± 0.40
GC (mM)	3.7 ± 2.0	3.4 ± 2.1	2.80 ± 0.89	2.3 ± 1.5	2.6 ± 1.1	2.1 ± 1.1	1.85 ± 0.99	1.37 ± 0.84
TCDC (mM)	1.48 ± 0.91	1.29 ± 0.76	1.00 ± 0.45	0.77 ± 0.66	0.94 ± 0.61	0.80 ± 0.56	0.67 ± 0.49	0.49 ± 0.44
UDC (mM)	1.2 ± 1.5	0.53 ± 0.50	0.36 ± 0.23	0.34 ± 0.29	028 ± 0.15	0.27 ± 0.20	0.17 ± 0.12	0.140 ± 0.095
GCDC (mM)	4.2 ± 2.4	3.9 ± 2.1	3.2 ± 1.0	2.7 ± 1.8	3.0 ± 1.4	2.4 ± 1.4	2.0 ± 1.2	1.5 ± 1.2
GDC (mM)	1.5 ± 0.6	1.70 ± 0.92	1.38 ± 0.74	1.27 ± 0.94	1.21 ± 0.74	0.97 ± 0.58	0.77 ± 0.41	0.46 ± 0.29
Total Bile Acids (mM)	13.1 ± 6.5	11.8 ± 5.9	10.1 ± 2.7	8.0 ± 5.1	8.9 ± 4.0	7.3 ± 3.9	6.1 ± 3.3	4.4 ± 3.1

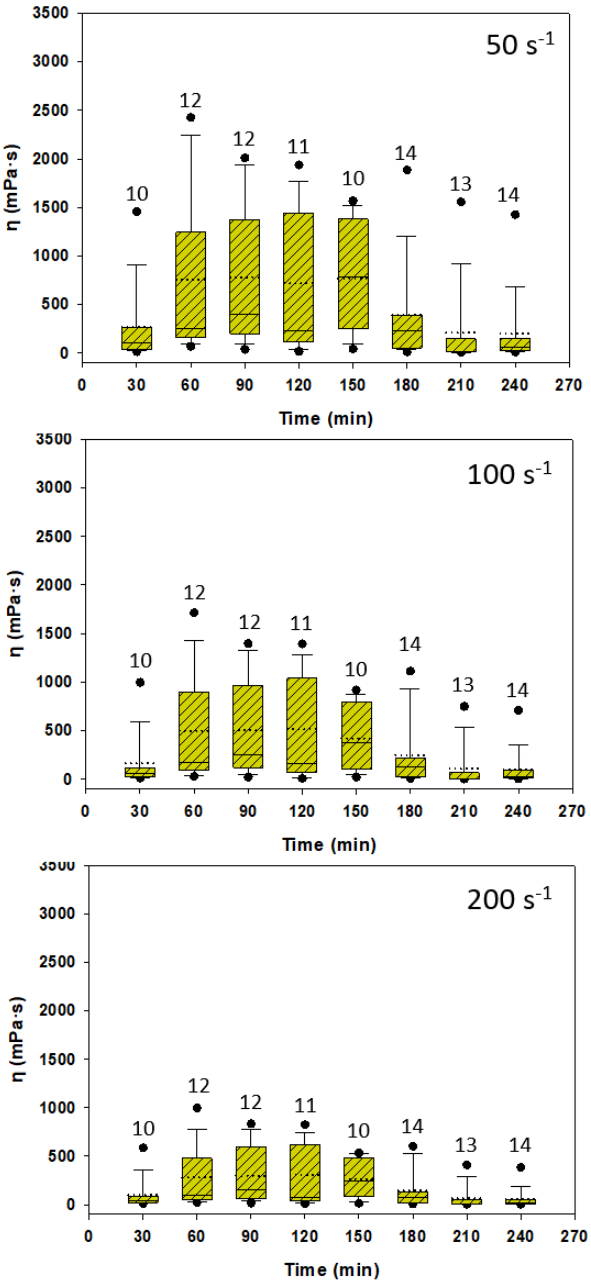

Figure C.10: Viscosity (37 °C) of contents in the upper small intestine after the standard meal.

Table C.8: Mean ± SD (n = 8-13) values for osmolality, concentrations of lipid species, and concentrations of bile acids in the micellar phase of contents in the upper small intestine after the standard meal.

Time (min)	30	60	90	120	150	180	210	240
Osmolality (mOsm/kg)	303 ± 71	335 ± 122	392 ± 101	339 ± 56	322 ± 41	293 ± 52	214 ± 56	200 ± 61
TGs (mM)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
DGs (mM)	0.22 ± 0.47	0.10 ± 0.10	0.091 ± 0.094	0.042 ± 0.048	0.028 ± 0.058	0.039 ± 0.078	0.039 ± 0.090	< 0.001
MGs (mM)	0.79 ± 0.49	0.7 ± 1.3	0.35 ± 0.54	0.29 ± 0.34	0.18 ± 0.19	0.20 ± 0.23	0.25 ± 0.23	0.19 ± 0.30
FAs (mM)	8.0 ± 7.4	3.1 ± 2.4	2.0 ± 1.7	2.2 ± 1.9	1.4 ± 1.3	1.5 ± 1.3	2.1 ± 1.8	1.03 ± 0.92
egg-PC (mM)	0.24 ± 0.25	0.15 ± 0.12	0.14 ± 0.11	0.15 ± 0.12	0.12 ± 0.11	0.078 ± 0.056	0.074 ± 0.075	0.052 ± 0.056
lyso-PC (mM)	2.0 ± 1.4	0.90 ± 0.91	0.64 ± 0.81	0.61 ± 0.54	0.50 ± 0.62	0.35 ± 0.52	0.60 ± 0.54	0.30 ± 0.32
CHO (mM)	0.94 ± 0.78	0.41 ± 0.46	0.24 ± 0.30	0.17 ± 0.14	0.134± 0.14	0.12 ± 0.14	0.18 ± 0.17	0.10 ± 0.12
TC (mM)	1.05 ± 0.88	0.56 ± 0.38	0.45 ± 0.25	0.60 ± 0.45	0.45 ± 0.32	0.50 ± 0.36	0.57 ± 0.51	0.37 ± 0.29
GC (mM)	3.6 ± 2.4	2.1 ± 2.2	1.8 ± 1.6	1.8 ± 1.1	1.44 ± 0.88	1.47 ± 0.91	1.5 ± 1.1	0.99 ± 0.70
TCDC (mM)	1.3 ± 1.2	0.52 ± 0.45	0.31 ± 0.29	0.42 ± 0.38	0.32 ± 0.21	0.31 ± 0.31	0.53 ± 0.50	0.26 ± 0.22
UDC (mM)	0.41 ± 0.40	0.18 ± 0.17	0.13 ± 0.13	0.15 ± 0.16	0.12 ± 0.11	0.094 ± 0.092	0.19 ± 0.12	0.083 ± 0.061
GCDC (mM)	4.2 ± 3.5	2.0 ± 2.2	1.3 ± 1.8	1.3 ± 1.1	1.06 ± 0.83	0.9 ± 1.0	1.4 ± 1.2	0.68 ± 0.67
GDC (mM)	1.9 ± 1.5	1.0 ± 1.3	0.8 ± 1.2	0.60 ± 0.68	0.54 ± 0.60	0.34 ± 0.46	0.43 ± 0.32	0.32 ± 0.33
Total Bile Acids (mM)	12.5 ± 9.4	6.3 ± 6.5	4.7 ± 5.0	4.9 ± 3.6	3.9 ± 2.6	3.7 ± 2.8	4.7 ± 3.5	2.6 ± 2.1

C.4. Implications for the *in vitro* drug product performance testing conditions

C.4.1. Composition of media simulating the fed state conditions in the upper GI lumen

Based on the physicochemical data collected in this work, composition of media for different levels of simulation of the environment in the fed stomach and upper small intestine was either confirmed or alterations were suggested (Pentafragka *et al*., 2020b).

With regards to Level I simulation, the observed median pH values and mean buffer capacity values in the antrum and upper small intestine only had small fluctuations over time (Figure C.7), therefore, applying one medium per region would be enough. Level I FeSSGF$_{late}$ and Level I FeSSIF-V2 proposed by Markopoulos, Andreas *et al*., 2015 adequately reflect the pH and buffer capacity of gastric contents and contents of the upper small intestine after the standard meal, respectively. FeSSGF$_{late}$ was suggested to be termed Level I FeSSGF-V2 (Table C.9) (Pentafragka *et al*., 2020b).

For Level II simulation, a single Level II biorelevant medium could be appropriate for representing average conditions over time, since fluctuations of mean osmolality and lipid species values are again small. Level II FeSSGF$_{late}$ reflects the osmolality and total molar concentration of lipid species in gastric contents observed in the present study, as it is isosmotic and contains a total of 14.5 mM lipid species (13.7 mM TGs, 0.044 mM FA and 0.674 mM PC), based on the amount of Lipofundin® employed for its preparation. Level II FeSSGF$_{late}$ was suggested to be termed Level II FeSSGF-V2 (Table C.9).

Level II FeSSIF-V2 slightly underestimates the total lipid and bile acid content in the upper small intestine and slightly overestimates relevant species in the micellar phase of aspirated samples. However, the use of its lipid and bile acid composition, after replacing PC with lyso-PC, was recommended, in order to avoid the formation of emulsions (Jantratid *et al*., 2008). The question of including cholesterol and, at least partly, replacing taurocholate with glycocholate was also raised for further investigation.

Level II simulation of the aqueous phase of gastric contents or the micellar phase of contents in the upper small intestine may need to be considered when drug transport towards the intestinal mucosa is to be investigated. Although drug absorption from the stomach is believed to be negligible in most cases, it may be possible for certain drugs (Buckley *et al*., 2018). A Level II FeSSGF$_T$ medium was suggested to simulate the conditions under which transport to the gastric mucosa could occur (Table C.9). Also, suggestions for the reparation of a Level II FeSSIF$_T$ medium for the simulation of the micellar phase of contents in the upper small intestine were

made, however, until the proposed composition is tested and proven adequately stable and compatible with the cell cultures, the use of previously proposed FeSSIF-TM_{Caco} (Markopoulos *et al*., 2014), is recommended.

Finally, based on viscosity data collected for the first time in aspirates from the upper GI lumen in this study, the basis for investigating the potential impact of increased luminal viscosity on oral drug absorption in the fed state can be set. It was suggested that Level III biorelevant media simulating the environment in the fed stomach should have a viscosity of about 800 mPa·s, at 100s-1 whereas Level III biorelevant media simulating the environment in the upper small intestine should be about 400 mPa·s at 100 s-1.

Table C.9: Biorelevant media simulating the gastric contents (FeSSGF-V2) and the aqueous phase of gastric contents ($FeSSGF_T$) during the first 3.5 hours, after initiation of administration of the standard meal. Level I simulation results after eliminating the bold cells in the table.

	FeSSGF-V2*	**$FeSSGF_T$**
TGs (mM)	**13.7****	**-**
Phosphatidylcholine (mM)	**0.674****	**0.5**
Sodium oleate (mM)	**0.044****	**0.2**
Ortho-phosphoric acid (mM)	5.5	5.5
Sodium dihydrogen phosphate (mM)	32	32
HCl/NaOH	qs pH3	qs pH3
Sodium Chloride (mM)	**127.5**	**127.5**
pH	3	3
Buffer capacity [(mmol/L)/ΔpH)]	25	25
Osmolality (mOsm/kg)	**300**	**300**
Viscosity at 100 s^{-1} (Level III)	**800 mPa·s**	**-**

*Identical to $FeSSGF_{late}$ proposed by Markopoulos, Andreas *et al*. 2015
**Included by using Lipofundin, 4.5% v/v

C.4.2. Usefulness of TIM-1 in reproducing drug disposition and characteristics of contents in the upper GI lumen after the standard meal

Data from TIM-1 experiments are presented in Appendix IX.

C.4.2.1. Disposition of highly permeable drugs in the gastric, duodenal and jejunal compartments of TIM-1

Paracetamol total amounts per volume of contents in the gastric, duodenal, and jejunal TIM-1 compartments versus human gastric and upper small intestinal paracetamol data are presented in Figure C.11. Intra- and inter-laboratory variability was low. Paracetamol total amounts per volume of contents in the gastric compartment of TIM-1 declined over time in an apparent zero-order manner, unlike with the apparently first-order decline in adults (Figure C.4). Overall, TIM-1 data in the gastric compartment seem to be in line with antral data in adults; a slight overestimation of the suspension data in adults at times between 75 and 135 minutes may be related to differences in the apparent kinetics of the decline between TIM-1 (zero order) and adults (first order).

Total amounts per volume in the duodenal compartment and in the jejunal compartment of TIM-1 peaked at 60-90 min and at 90-120 min, respectively, in contrast to the upper small intestine of humans (Figures C.11-F). This discrepancy may be related to differences in drug gastric emptying, upper small intestinal transit and/or radial transport kinetics. At times between 90 and 120 minutes, data in the duodenal TIM-1 compartment slightly overestimated data in adults (Figure C.11-C and C.11-D). TIM-1 jejunal data are closer than TIM-1 duodenal data to adult data in the upper small intestine (Figure C.11-D and C.11-F), likely due to the presence of the filter in the TIM-1 jejunal compartment, simulating the radial drug transport through the intestinal wall.

Danazol total amounts per volume of contents in the gastric, duodenal, and jejunal TIM-1 compartments versus human gastric and upper small intestinal danazol data are presented in Figure C.12. Intra-laboratory variability of TIM-1 drug disposition data was very low. As in adults, danazol total amounts per volume of contents in the TIM-1 gastric compartment over time did not show a consistent trend (Figure C.12-A and C.12-B), however, they peaked at 135 min, after the sunflower oil solution, and at 180 min (time at which the housekeeper wave was induced), after the suspension. The peak at 135 minutes may relate to the specific mixing conditions in the TIM-1 gastric compartment. Recently, an advanced TIM-1 gastric compartment with different hydrodynamics (TIM-agc) has been introduced by The TIM company (Minekus, 2015). In the duodenal and jejunal compartments, danazol total amounts

per volume peaked at slightly longer times than in the gastric compartment (hardly visible in the jejunal compartment). TIM-1 jejunal data were generally in line with data in the human upper small intestine.

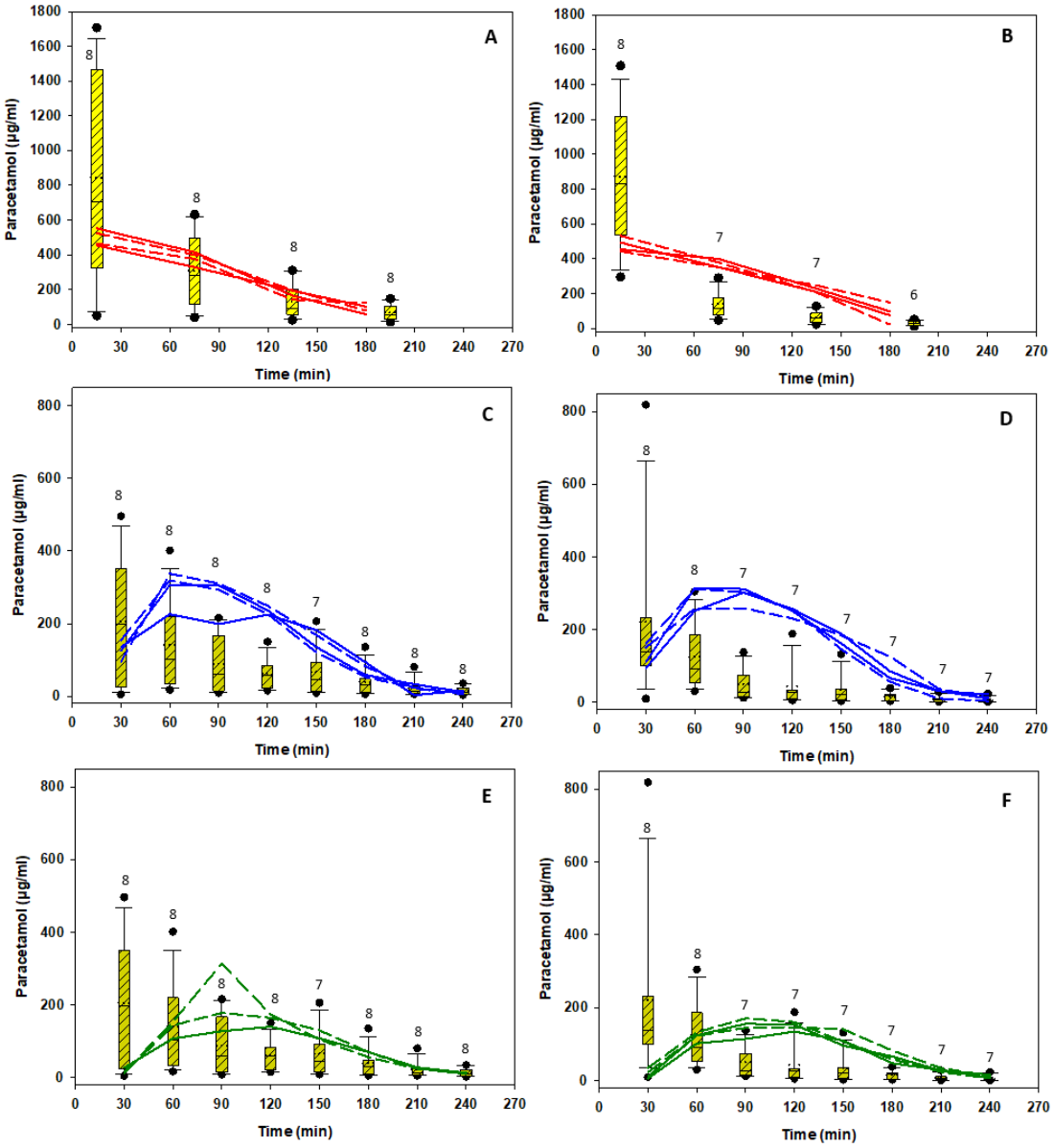

Figure C.11: Paracetamol total amount per volume of contents in the gastric compartment (A, B), duodenal compartment (C, D), and jejunal compartment (E, F) of TIM-1 model, after administration of aqueous solution (left panel) and aqueous suspension (right panel) in the TIM-1 gastric compartment [individual data from Pfizer (continuous lines) and from the TIM company (dashed lines)] vs. data in antral contents (A, B - box plots) and contents of the upper small intestine of adults (C, D, E, F - box plots).

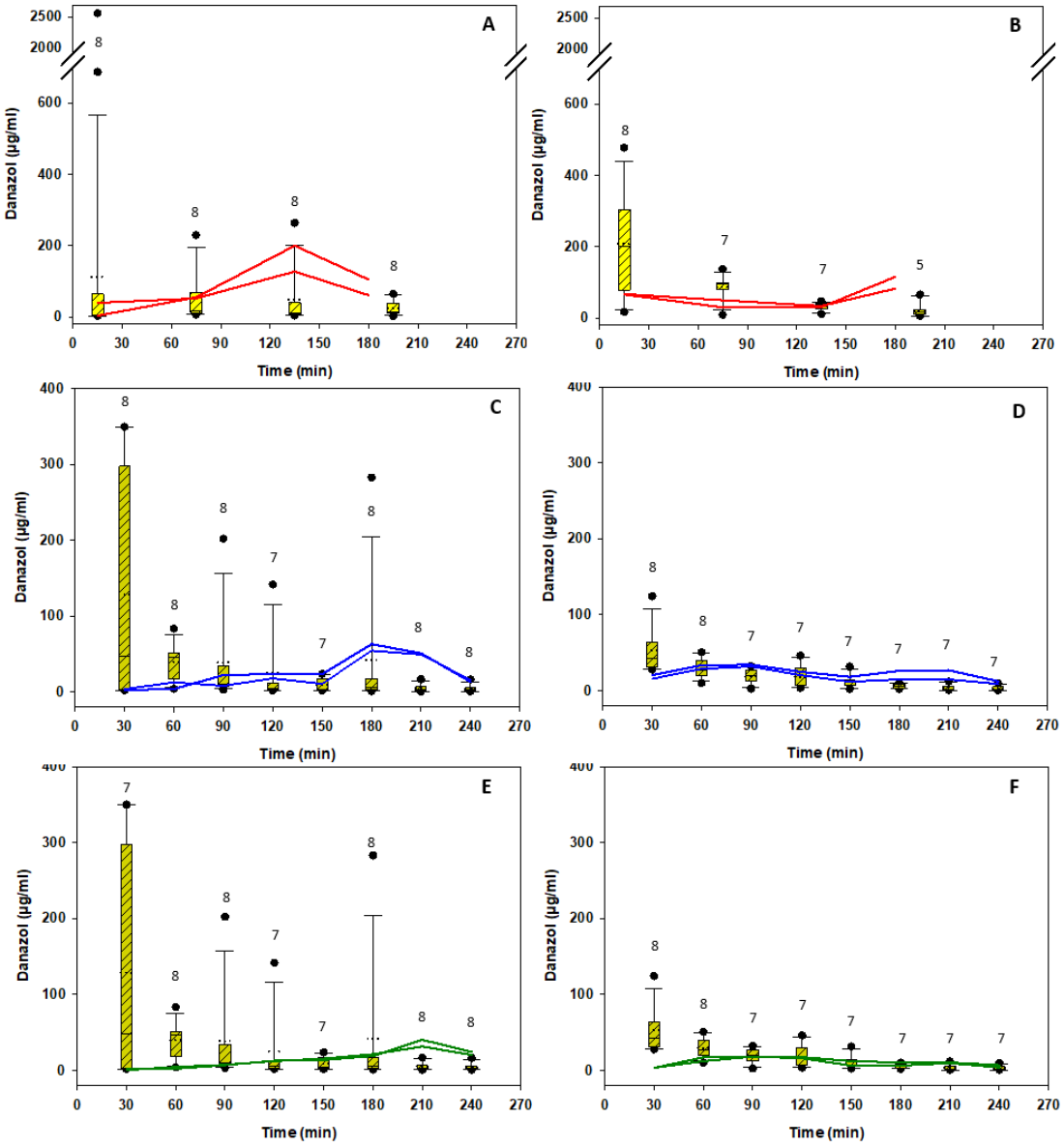

Figure C.12: Danazol total amounts per volume of contents in the gastric compartment (A, B), duodenal compartment (C, D), and jejunal compartment (E, F) of TIM-1 model, after administration of sunflower oil solution (left panel) and aqueous suspension (right panel) in the TIM-1 gastric compartment [individual data from the TIM company (continuous lines)] vs. data in antral contents (A, B - box plots) and contents of the upper small intestine of adults (C, D, E, F - box plots). One outlier in the upper small intestinal human data [2087.5 µg/mL at 30 min] is not shown in the graph (B, C, E, F) to improve visibility.

C.4.2.2. Physicochemical characteristics of contents in the gastric, duodenal and jejunal compartments of TIM-1

Phenol red total amounts per volume of contents in the gastric and duodenal TIM-1 compartments versus data from the adult antrum and upper small intestine are presented in Figure C.13. Data from the jejunal compartment of TIM-1 are not considered since phenol red was eliminated through the filter whereas it is not absorbed in the human GI tract. Total amounts per volume were generally in line with human data.

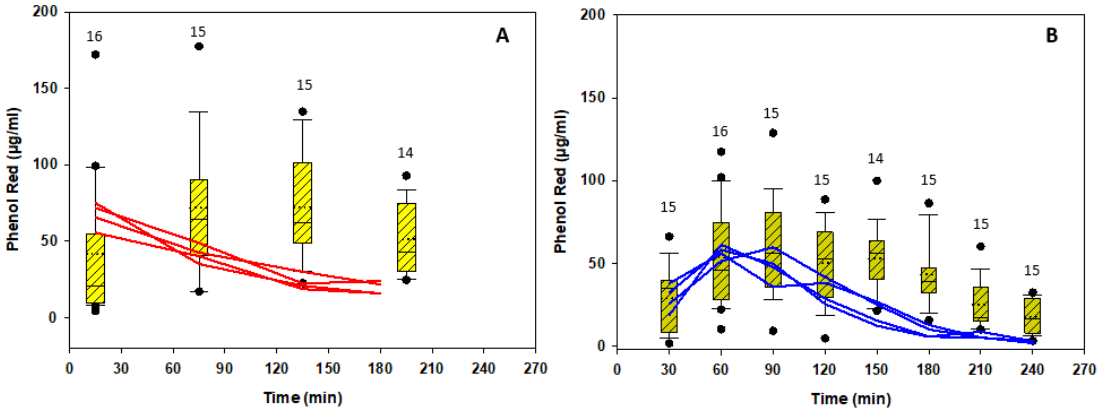

Figure C.13: Phenol red total amount per volume of contents in the gastric compartment (A) and duodenal compartment (B) of TIM-1 model (continuous lines, individual data, n=4) vs. data in antral contents (A - box plots) and contents of the upper small intestine of adults (B - box plots).

pH in the gastric, duodenal, and jejunal TIM-1 compartments versus data from the adult antrum and upper small intestine are presented in Figure C.14. pH in the gastric compartment slightly overestimated human pH at 30 min and returned to values lower than 2 at about two hours (Figure C.14-A). One reason for the faster return to fasted state conditions could be the smaller amount of the meal employed in TIM-1 experiments (30% compared to the meal administered to adults) and the subsequent faster completion of gastric emptying of the meal [3 hours post dosing at TIM-1 compared to 4-8 hours, after ingestion of the standard meal in adults (Koziolek *et al.*, 2014b)]. pH values in the duodenal compartment were in line with human data whereas in the jejunal compartment they slightly overestimated luminal data in the upper small intestine of adults at times between 120 and 180 min.

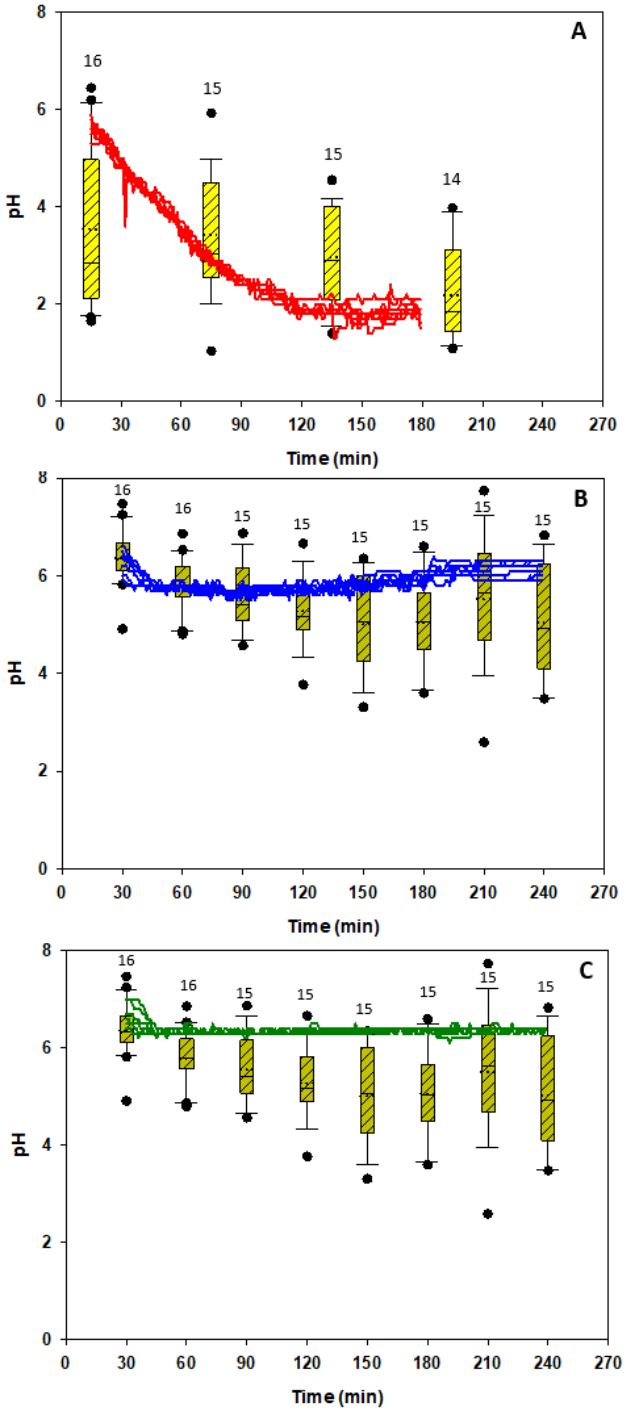

Figure C.14: pH of contents in the gastric compartment (A), duodenal compartment (B) and jejunal compartment (C) of the TIM-1 model (continuous lines, individual data, n=8) vs. pH in antral contents(A - box plots) and contents of the upper small intestine of adults (B - box plots).

Concentrations of lipid species in total contents of the gastric compartment of TIM-1 over time after initiation of the experiment are graphically presented in Figure C.15. Especially after the first 15 min, TGs and DGs concentrations in the gastric compartment of TIM-1 underestimated the presence of these species in the antrum of adults. MGs and FAs concentrations are

generally in line with adult data (Figure C.15-C and C.15-D). It is not known if TG species in the lipid components of the high-fat high-calorie meal employed in TIM-1 (margarine) are identical to TG species in lipid components of the standard meal (butter and sunflower oil). Quantification of TGs, DGs, MGs, and FAs species in samples from the TIM-1 experiments and in aspirates from the clinical study was performed by applying the same analytical methods (Appendix III) and by using standards that reflect the major TGs, DGs, MGs, and FAs in the standard meal. Total CHO and PC content is only slightly underestimated.

Concentrations of lipid species in total contents and the micellar phase of contents of the duodenal compartment and the jejunal compartment are presented in comparison with data from the upper small intestine of adults in Figures C.16 and C.17. With regards to TGs, DGs, MGs, and FAs, comments similar with those made for the corresponding data in Figure C.15 can be made. The lower FAs concentrations in the total contents of the duodenal compartment of TIM-1 vs. the total contents of the adults' upper small intestine and the similar concentrations in the micellar phase of TIM-1 and adults (Figure C.16-D) provide additional evidence for potential differences in the identity of FAs in the TIM-1 meal and the standard meal. CHO and PC concentrations in the TIM-1 duodenal compartment are generally in line with data in adults (total contents) or slightly over-estimated (micellar phase).

In the jejunal compartment of TIM-1 lipid species data were roughly similar to those in the duodenal compartment (Figure C.17), suggesting no major impact of the presence of filter in the jejunal compartment on the luminal disposition of lipid species.

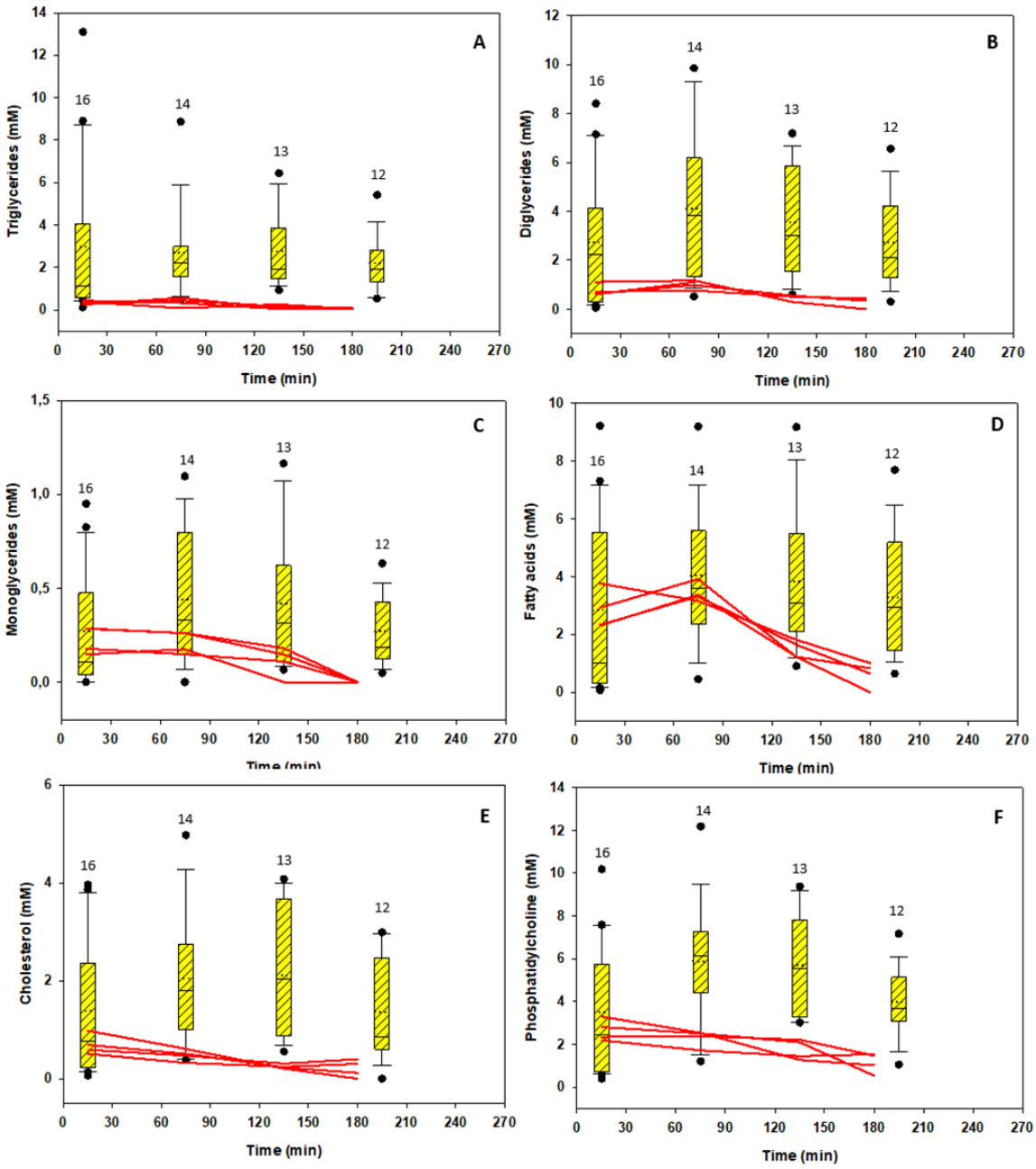

Figure C.15: Total lipid species amounts per volume in the gastric compartment of TIM-1 model (continuous lines, individual data, n=4) vs. data in antral contents of adults (boxplots). A: triglycerides, B: diglycerides, C: monoglyceride, D: fatty acids, E: cholesterol, F: phosphatidylcholine.

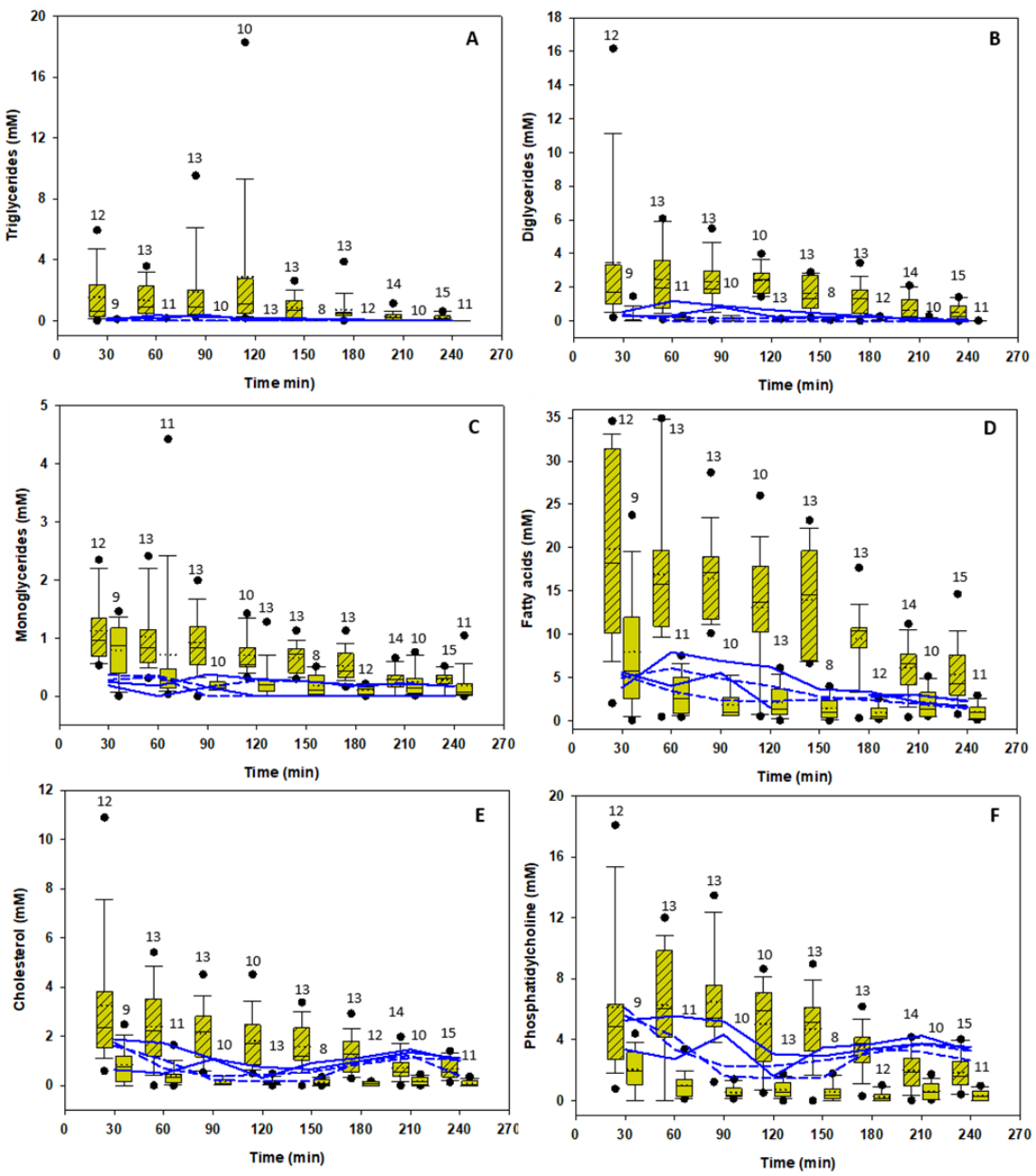

Figure C.16: Individual data (n=2) of lipid species in the duodenal compartment of TIM-1 model [total amounts per volume (continuous lines); concentrations in the micellar phase (dashed lines)] vs. data of contents in the upper small intestine of adults [total amounts per volume (lined boxplots); concentrations in the micellar phase (empty boxplots)] A: triglycerides, B: diglycerides, C: monoglyceride, D: fatty acids, E: cholesterol, F: phosphatidylcholine.

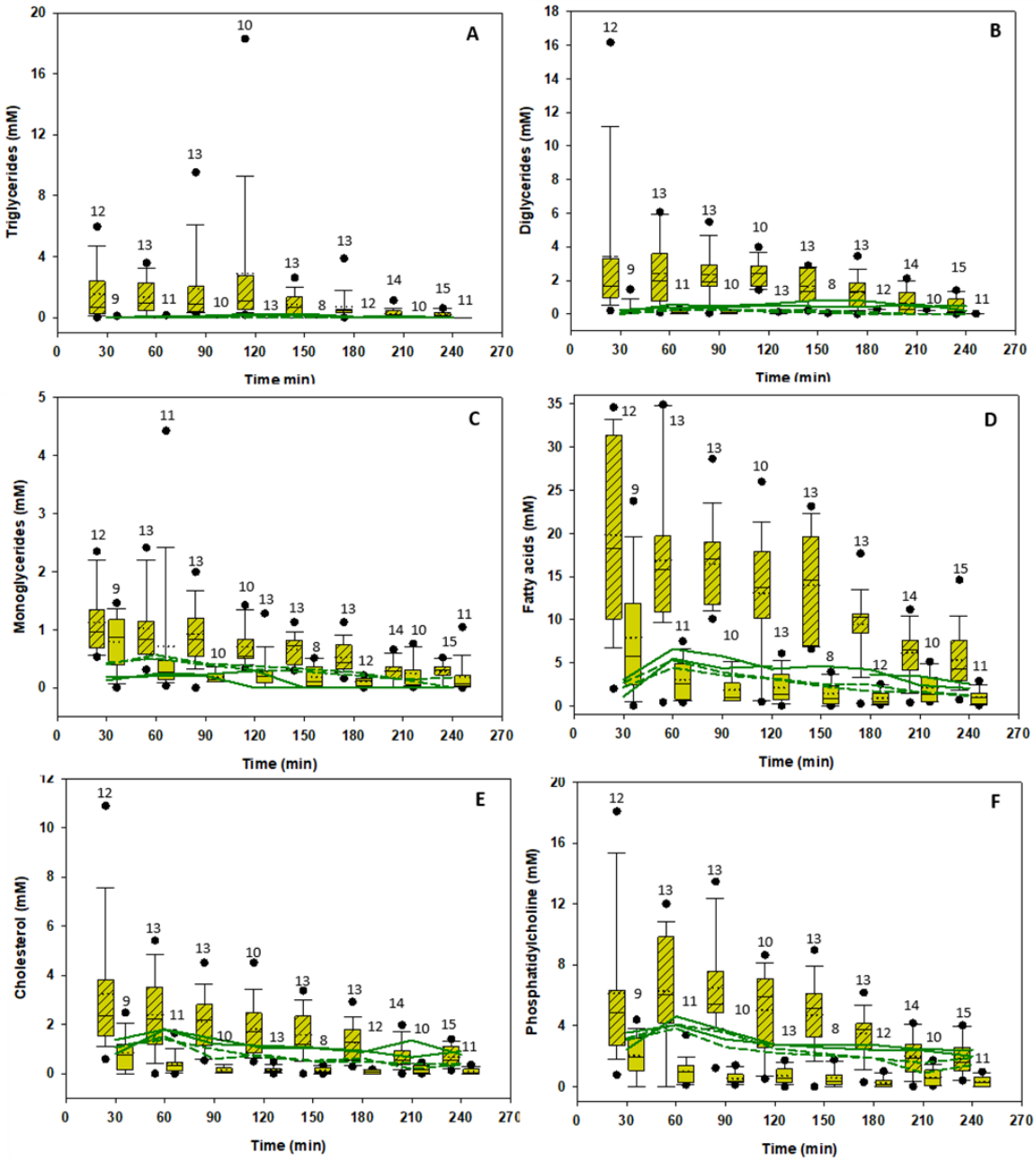

Figure C.17: Individual data (n=2) of lipid species in the jejunal compartment of TIM-1 model [total amounts per volume (continuous lines); concentrations in the micellar phase (dashed lines)] vs. data of contents in the upper small intestine of adults [total amounts per volume (lined boxplots); concentrations in the micellar phase (empty boxplots)] A: triglycerides, B: diglycerides, C: monoglyceride, D: fatty acids, E: cholesterol, F: phosphatidylcholine.

Total bile acid content of the porcine bile solution secreted at a rate of 0.5 mL/min in the duodenal compartment of TIM-1 was measured to be 26.4 ± 1.8 mM. In the jejunal compartment an enzyme solution containing 10% of the bile solution is constantly secreted at a rate of 2.8 mL/min.

About half of the individual bile acid content in porcine bile that is used in TIM-1 experiments (GCDC, TCDC and TC) was found to be identical to half of the individual bile acid content in the upper small intestine of adults (Figure C.18). The second half in porcine bile consisted of GHDC and GHC whereas the second half in the contents of the human upper small intestine consisted of GDC, GC and UDC (Figure C.18). However, the ratio of taurine to glycine conjugates is similar in porcine bile and in the contents of upper small intestine of adults (Figure C.18). Data on bile acids' identity and percentages in porcine bile used in TIM-1 are in line with previous findings (Effinger, 2020).

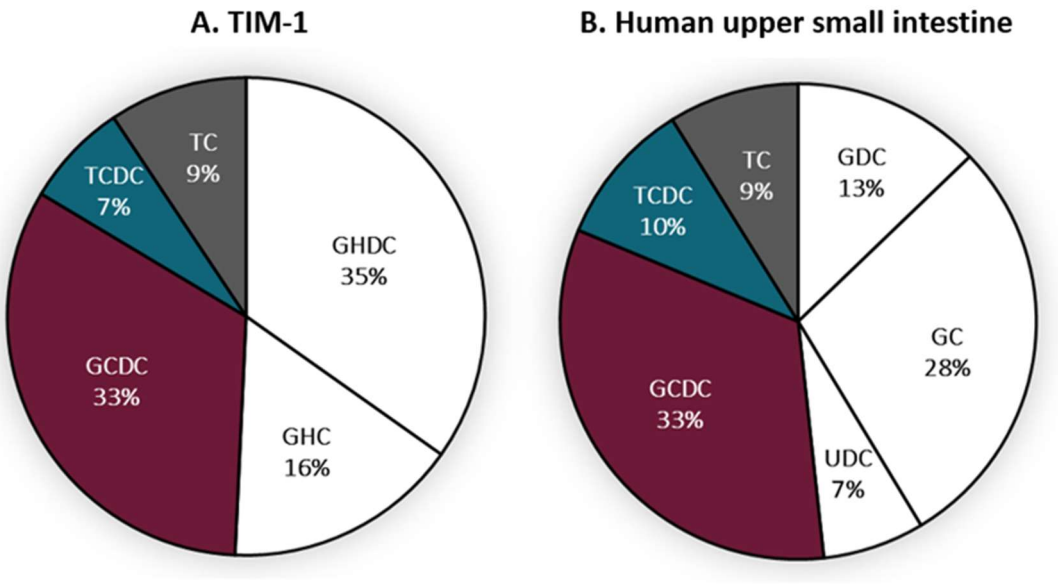

Figure C.18: Individual bile acids quantified in porcine bile used in TIM-1 model (A) vs. individual bile acids in the human upper small intestine (B). Bile acids that are present in TIM-1 but not in the upper small intestine of adults and vice versa have no colored background. GCDC: glycohenodeoxycholic acid, TCDC: taurochenodeoxycholic acid, TC: taurocholic acid, GDC: glycocholic acid, UDC: ursodeoxycholic acid, GC: glycochlic acid, GHDC: glycohyodeoxycholic acid, GHC: glycohyocholic acid.

During the first 120 min after initiation of the experiment, total bile acid concentrations in the duodenal or the jejunal compartment slightly overestimated concentrations in the upper small intestine of adults (Figure C.19). At later time points total bile acids concentrations increased, in contrast to a trend of decreasing total bile acids concentration in the upper small intestine

of adults (Figure C.19). The constant bile flow during the entire TIM-1 experiment [unlike the bile secretion rates after meal in adults (Lawson *et al.*, 1983)] may be one reason for the increased concentrations after 120min.

Total bile acids concentrations in the micellar phase of contents of the duodenal and jejunal compartments followed a similar pattern with concentrations in total contents, i.e. they increased at times later than 120 min (Figure C.19). However, unlike concentrations in total contents, they greatly overestimated micellar concentrations in the upper small intestine of adults (Figure C.19). This could be attributed to the higher hydrophilicity of the glycohyodeoxycholic acid and hyocholic acid in the porcine bile as compared to glycodeoxycholic and ursodeoxycholic acid in humans (Roda *et al.*, 1990).

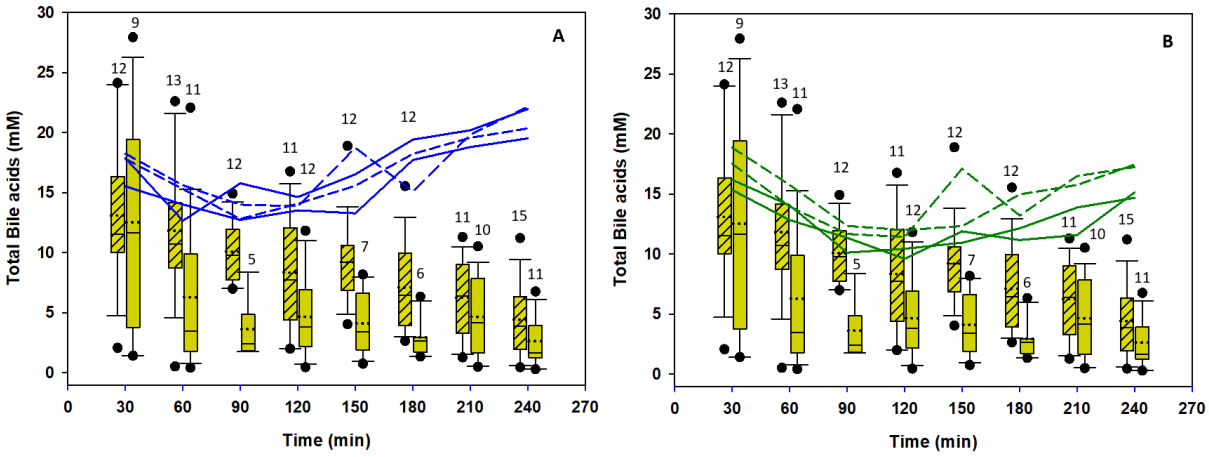

Figure C.19: Individual data (n=2) of total bile acids (sum of individual bile acids) in the duodenal compartment (A) and jejunal compartment (B) of TIM-1 model [total amounts per volume (continuous lines); concentrations in the micellar phase (dashed lines)] vs. total bile acids in contents of the upper small intestine of adults [total amounts per volume (lined boxplots); concentrations in the micellar phase (empty boxplots)]

D. CONCLUSIONS

Based on data collected in this study:

1. For non-ionizable BCS Class I drugs administered as IR solid dosage forms after the standard meal, apparent concentrations in the aqueous contents of the stomach are higher than apparent concentrations in the micellar contents of the upper small intestine. Gastric emptying follows apparent first-order kinetics and rates are slower than in the fasted state. For non-ionizable BCS Class II drugs administered as IR solid dosage forms after the standard meal, apparent concentrations in the aqueous contents of the stomach are lower than apparent concentrations in the micellar contents of the upper small intestine. Gastric emptying is expected to be highly variable, after disintegration of a capsule containing the drug in long-chain triglyceride solution. If the dosage form disintegrates to solid particles, gastric emptying is expected to follow apparent first-order kinetics and rates seem to be slower than BCS Class I drugs.

2. In the antrum, composition of contents over time after the standard meal administration fluctuated less than after liquid meals with similar caloric content. Viscosity of contents after the standard meal is 80-800 times higher than in the fasted state. In the upper small intestine viscosity of contents after the standard meal is at least 100 times higher than in the fasted state. Differences in composition between the aqueous phase and total gastric contents and between the micellar phase and total contents in the upper small intestine after administration of the standard meal were documented for the first time.

3. Level I and Level II biorelevant media simulating the intragastric conditions can be simplified, whereas FeSSIF-V2 composition was confirmed to be representative of the composition of the micellar phase of contents in the upper small intestine. Representative values of viscosity levels in the stomach and in the upper small intestine and Level II simulation of the aqueous phase of gastric contents after the standard meal, were proposed for first time.

4. After scaling down the human single dose to match the scaling down of the meal volume in TIM-1, average paracetamol and danazol total amounts per volume of gastric contents and contents in the upper small intestine were adequately simulated by data in the gastric compartment and in the jejunal compartment of TIM-1, respectively. Secretion rates of

bile acids in the duodenal and jejunal compartment require optimization. Sourcing an alternative bile acid solution to improve distribution of individual bile acids in the micellar phase of duodenal and jejunal contents is also recommended.

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APPENDICES

APPENDIX I Copies of the Approvals from the Scientific and Executive Committees of the Red Cross Hospital of Athens and Copy of the Certificate of Insurance of Investigators and Volunteers

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
ΥΠΟΥΡΓΕΙΟ ΥΓΕΙΑΣ
ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ
ΚΟΡΓΙΑΛΕΝΕΙΟ ΜΠΕΝΑΚΕΙΟ Ε.Ε.Σ. Σ
ΕΠΙΣΤΗΜΟΝΙΚΟ ΣΥΜΒΟΥΛΙΟ
Αρ. Πρωτ.: 165

18 Σεπτεμβρίου 2017

ΠΡΟΣ
ΤΗ ΓΡΑΜΜΑΤΕΙΑ ΤΟΥ Δ.Σ.

ΘΕΜΑ: Έγκριση μελέτης.

Το Επιστημονικό Συμβούλιο του Νοσοκομείου αφού έλαβε υπόψη την αίτηση του Διευθυντή, Επιστημονικά Υπεύθυνου, του **Γαστρεντερολογικού τμήματος κ. Γκούμα Κων/νου**, με αριθ. Πρωτ. **20505/ 13-9-2017** για **έγκριση μελέτης** υπό την εποπτεία του με τίτλο « Συγκέντρωσης παρακεταμόλης και δαναζόλης στον ανώτερο γαστρεντερικό αυλό μετά από χορήγηση σε υγρή και στερεή κατάσταση κατά τη διάρκεια της λέψης και φυσικοχημικός χαρακτηρισμός των ενδοαυλικών περιεχομένων», στο Γαστρεντερολογικό τμήμα του Νοσοκομείου,

Εισηγείται

Θετικά για την έγκριση μελέτης. Δεν υπάρχει οικονομική επιβάρυνση για το Νοσοκομείο μας.

Ο ΠΡΟΕΔΡΟΣ
ΤΟΥ ΕΠΙΣΤΗΜΟΝΙΚΟΥ ΣΥΜΒΟΥΛΙΟΥ

ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ
ΚΟΡΓΙΑΛΕΝΕΙΟ ΜΠΕΝΑΚΕΙΟ Ε.Ε.Σ.
ΕΠΙΣΤΗΜΟΝΙΚΟ ΣΥΜΒΟΥΛΙΟ
ΠΡΟΕΔΡΟΣ: Α. ΚΑΤΣΙΒΑΣ
ΚΑΤΣΙΒΑΣ

Κοινοποιήσεις
- Γρ. Διοικητή
- Γαστρεντερολογικό Τμήμα

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
ΥΠΟΥΡΓΕΙΟ ΥΓΕΙΑΣ
ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ
«ΚΟΡΓΙΑΛΕΝΕΙΟ – ΜΠΕΝΑΚΕΙΟ» Ε.Ε.Σ
ΓΡΑΜΜΑΤΕΙΑ ΔΙΟΙΚΗΤΙΚΟΥ ΣΥΜΒΟΥΛΙΟΥ
Αριθμ. Πρωτ. 7935

ΑΠΟΣΠΑΣΜΑ ΠΡΑΚΤΙΚΟΥ

ΔΙΟΙΚΗΤΙΚΟΥ ΣΥΜΒΟΥΛΙΟΥ 6ης ΣΥΝΕΔΡΙΑΣΗΣ ΘΕΜΑ 37ο

Στην Αθήνα σήμερα 26 Φεβρουαρίου 2018 ημέρα Δευτέρα και ώρα 13.00μ.μ. συνήλθε σε συνεδρίαση το Διοικητικό Συμβούλιο, το οποίο συγκροτήθηκε με την υπ'αριθμ. Α22/Γ.Π 95919/16 Απόφαση του Υπουργείου Υγείας (ΦΕΚ279/Υ.Ο.Δ.Δ/13.6.1017), υπό την προεδρεία της Προέδρου του Δ.Σ. κας Βελέντζα- Ζουρούδη Ευαγγελίας για την λήψη αποφάσεων επί των θεμάτων της Ημερήσιας Διάταξης.

Στη συνεδρίαση εκλήθησαν όλα τα μέλη και παρευρέθησαν, ο Διοικητής και μέλος κ.Γεωργόπουλος Ευθύμιος καθώς και τα μέλη : κ. Αμοργιανού Μαρία, κ. Εμμανουήλ Κωττάκης, κ.Μπουρμπούλης Νικόλαος, κ. Παπαντωνίου Βασίλειος, κ.Μιχαήλ Τιμπισράνης , κ. Δημητρόπουλος Λεωνίδας καθώς και το αναπληρωματικό μέλος Ανδρουτσόπουλος Δημήτριος.

Στη συνεδρίαση συμμετείχε η Γραμματέας του Διοικητικού Συμβουλίου , Μαρία Κούρτη.

Θέμα 37ο: «Εγκριση Μελέτης του Διευθυντή , Επιστημονικά Υπεύθυνου του Γαστρεντερολογικού Τμήματος κου Γκούμα Κων/νου, με αρ.πρωτ. 20505/13.9.2017»

Το Δ.Σ έπειτα από διαλογική συζήτηση και έχοντας υπ' όψιν:

1) Το υπ'αριθμ 20505/13.9.2017 αίτημα του Διευθυντή – Επιστημονικά Υπεύθυνου του Γαστρεντερολογικού Τμήματος κου Γκούμα Κων/νου.

2) Την υπ' αριθμ.πρωτ.21276/22.9.2017 θετική εισήγηση του Επιστημονικού Συμβουλίου

ΑΠΟΦΑΣΙΖΕΙ

Εγκρίνει , ομόφωνα, το υπ' αριθμ. πρωτ.20505/13.9.2017 αίτημα του Διευθυντή – Επιστημονικά Υπεύθυνου του Γαστρεντερολογικού Τμήματος κου Γκούμα Κων/νου, που αφορά μελέτη με τίτλο «Συγκεντρώσεις παρακεταμόλης και δαναζόλης στον ανώτερο γαστρεντερικό αυλό μετά από χορήγηση σε υγρή και στερεή κατάσταση κατά τη διάρκεια της πέψης και φυσικοχημικός χαρακτηρισμός των ενδοαυλικών περιεχομένων».

Η ανωτέρω μελέτη δεν επιβαρύνει οικονομικά το Νοσοκομείο μας.

ΕΝΕΡΓΕΙΑ:

ΕΠΙΣΤΗΜΟΝΙΚΟ ΣΥΜΒΟΥΛΙΟ

ΚΟΙΝΟΠΟΙΗΣΗ:

ΓΡ.ΠΡΟΕΔΡΟΥ
ΓΡ. ΔΙΟΙΚΗΤΗ
ΓΡ.ΑΝ. ΔΙΟΙΚΗΤΗ
Δ/ΝΤΗΣ ΔΙΟΙΚ. ΥΠΗΡΕΣΙΑΣ
Δ/ΝΤΗΣ ΙΑΤΡΙΚΗΣ ΥΠΗΡΕΣΙΑΣ
Υ/Β/ΝΤΗΣ ΔΙΟΙΚ. ΥΠΗΡΕΣΙΑΣ
ΓΑΣΤΡΕΝΤΕΡΟΛΟΓΙΚΟ ΤΜΗΜΑ
ΓΡΑΜ. ΔΙΟΙΚ. ΣΥΜΒΟΥΛΙΟΥ

ΑΚΡΙΒΕΣ ΑΠΟΣΠΑΣΜΑ
ΑΘΗΝΑ 28 ΦΕΒΡΟΥΑΡΙΟΥ 2018

Η Γραμματέας του Δ.Σ
Μαρία Κρύπτη

2

Βεβαίωση Ασφαλιστικής Κάλυψης

Αθήνα, 30.11.2017

ΣΥΜΒΟΛΑΙΟ ΑΣΤΙΚΗΣ ΕΥΘΥΝΗΣ No. 390-01102081-14160 (Ασφάλιση Κλινικής Δοκιμής)

Βεβαιώνουμε ότι το ανωτέρω ασφαλιστήριο συμβόλαιο της HDI Global SE, Hellas καλύπτει την εκ του νόμου ευθύνη της κάτωθι αναφερόμενης ασφαλισμένης επωνυμίας και των κάτωθι συμμετεχόντων ερευνητών –οι οποίοι θεωρούνται συνασφαλιζόμενοι- κατά τις διατάξεις της παραγρ. 1στ του άρθρου 3 της Υ.Α. ΔΥΓ3/89292 της 30.12.03 (ΦΕΚ 1973/τ.Β'/31.12.03), την διευκρινιστική Εγκύκλιο του ΕΟΦ (22/11/2012, Αρ.Πρωτ.82798) και σύμφωνα με τους όρους της εταιρίας μας, όσον αφορά στην ακολούθως περιγραφόμενη κλινική δοκιμή.

Ασφαλισμένος:	ΕΘΝΙΚΟ & ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ / ΤΜΗΜΑ ΦΑΡΜΑΚΕΥΤΙΚΗΣ	
Τίτλος μελέτης:	Συγκεντρώσεις παρακεταμόλης και δαναζόλης στον ανώτερο γαστρεντερικό αυλό μετά από χορήγηση σε υγρή και στερεή κατάσταση κατά τη διάρκεια της πέψης και φυσικοχημικός χαρακτηρισμός των ενδοαυλικών περιεχομένων.	
Αριθμός πρωτοκόλλου	20505/13-09-2017	
Συνασφαλισμένοι συμμετέχοντες ερευνητές / Κέντρο διεξαγωγής της μελέτης:	Ερευνητική ομάδα	Νοσηλευτικό Ίδρυμα / κλινική
	-Χ.Ρέππας (επιστημονικός υπεύθυνος, Ερευνητής ΕΚΠΑ) -Μ.Βερτζώνη (Ερευνήτρια ΕΚΠΑ) -Κ.Γκούμας (Γαστρεντερολόγος ΝΕΕΣ, κλινικός υπεύθυνος) -Α.Λουρμπάκου (Ακτινολόγος ΝΕΕΣ) -Μ.Κώτογλου (χειρίστρια ακτινοσκοπίου ΝΕΕΣ) -Χ.Πενταφράγκα (Ερευνήτρια ΕΚΠΑ)	Κοργιαλένειο-Μπενάκειο Νοσοκομείο Ελληνικού Ερυθρού Σταυρού/Γαστρεντερολογικό Τμήμα (Αθανασάκη & Ερυθρού Σταυρού 1, τκ 11526, Αθήνα)(ΝΕΕΣ)

HDI Global SE, Hellas
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ΑΡ. ΓΕΜΗ: 123913101001
ΑΦΜ : 098087915 – ΔΟΥ: ΦΑΕ Αθηνών

Βεβαίωση Ασφαλιστικής Κάλυψης

Αριθμός συμμετεχόντων εθελοντών:	8		
Περίοδος ασφαλιστικής κάλυψης:	Από: 01/01/2018	Έως:	31/05/2019
Όρια αποζημιώσεως:	EUR 300.000,00	ανά ασθενή	
	EUR 5.000.000,00	συνολικά για το ασφαλισμένο πρωτόκολλο της κλινικής δοκιμής	

Για την Εταιρία,
HDI Global SE, Hellas
Τμ.Αστικής Ευθύνης

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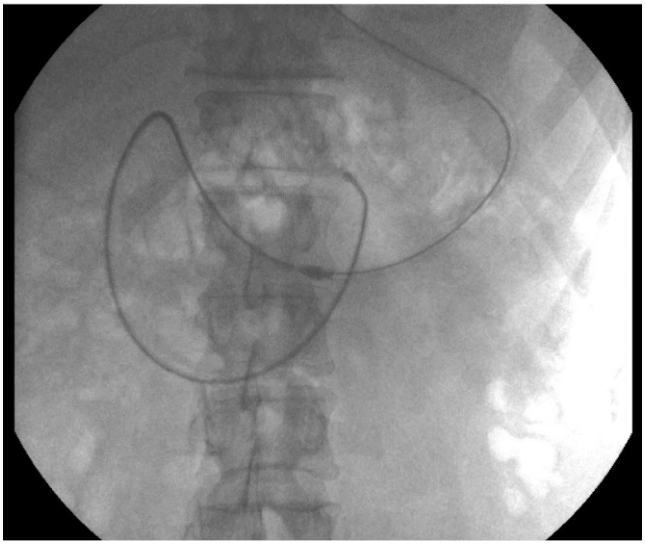
Ελίνα Παπασπυροπούλου

Αγγελική Ζαχαριαδάκη

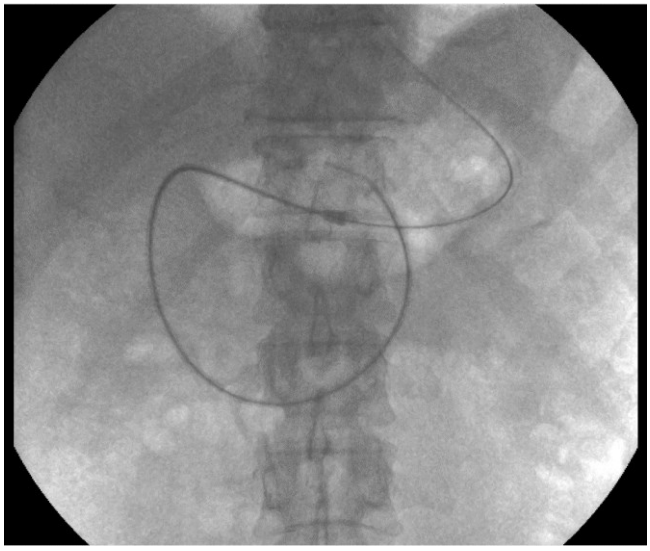
APPENDIX II Copies of the fluoroscopic illustrations taken in the beginning of the clinical day to verify the correct positioning of the GI tube

Volunteer # 1

Phase I

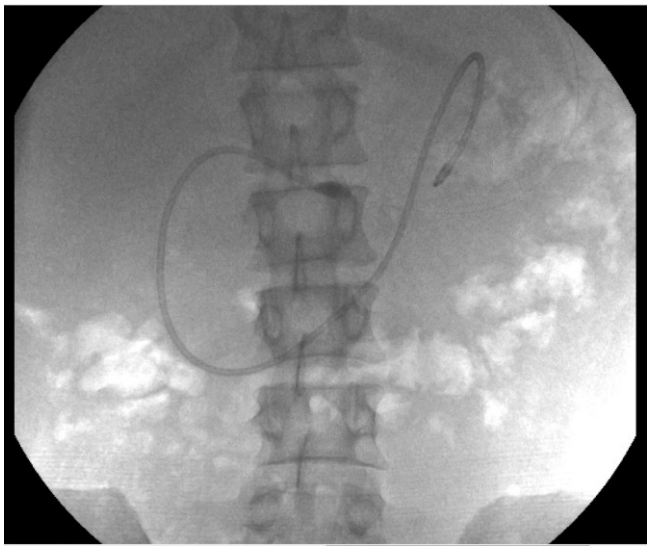


Phase II

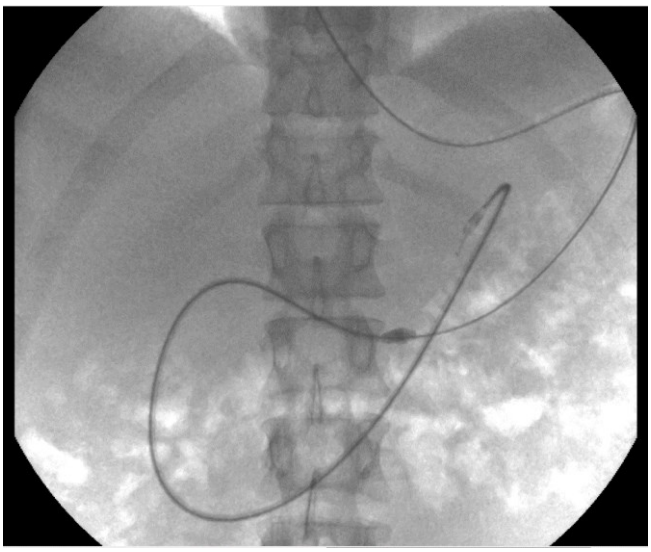


Volunteer # 2

Phase I

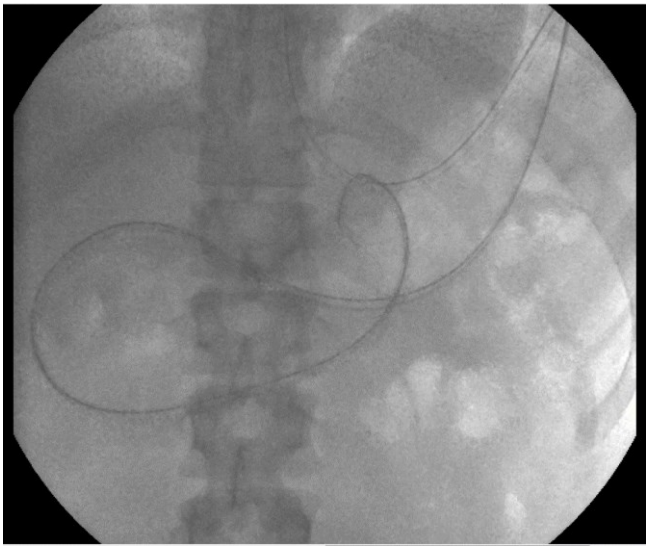


Phase II

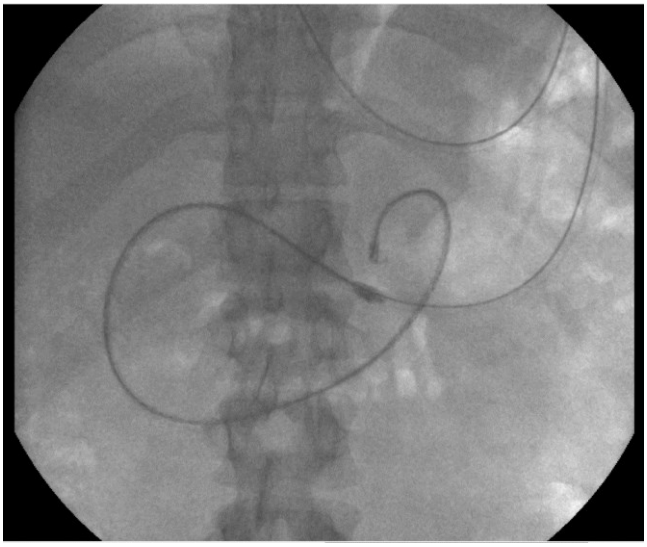


Volunteer # 3

Phase I

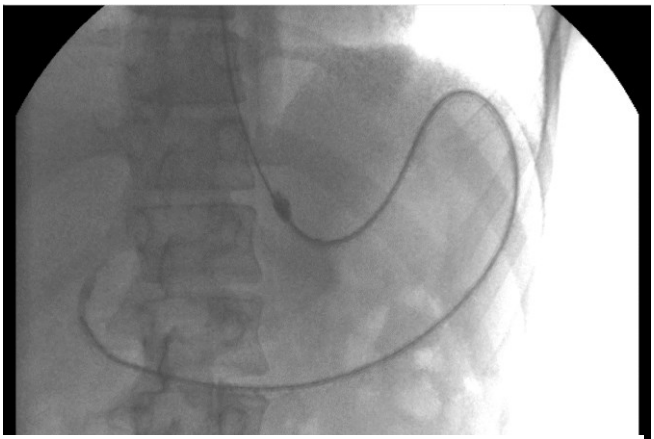


Phase II



Volunteer # 4

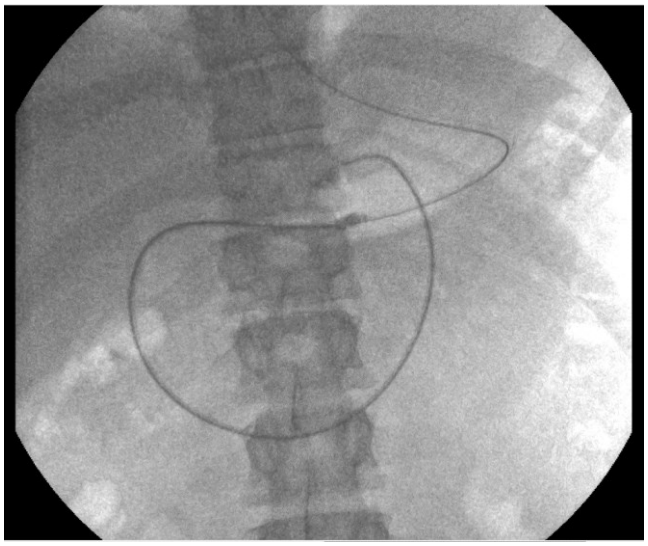
Phase I



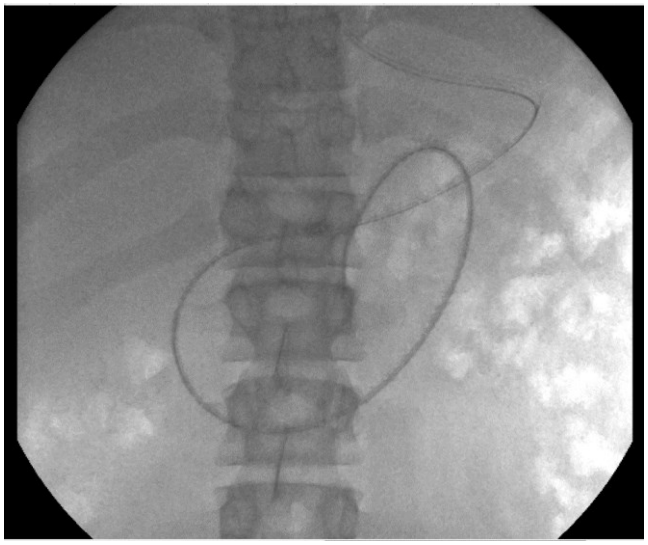
Unsuccessful positioning of the tube - inability to pass into the duodenum due to stomach anatomy.

Volunteer # 5

Phase I

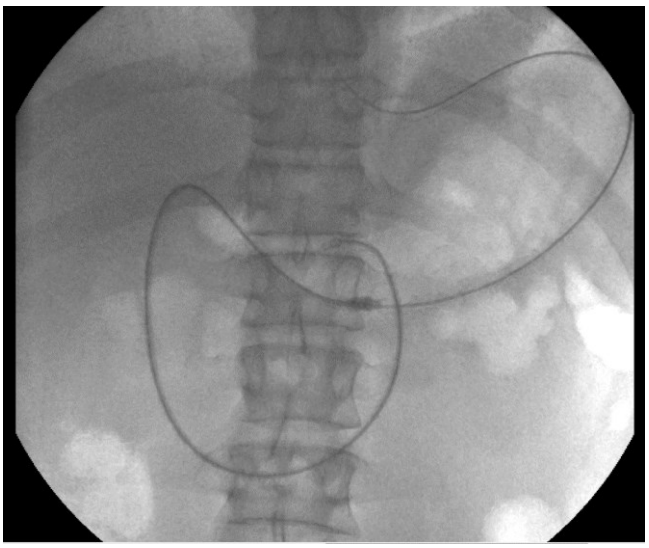


Phase II

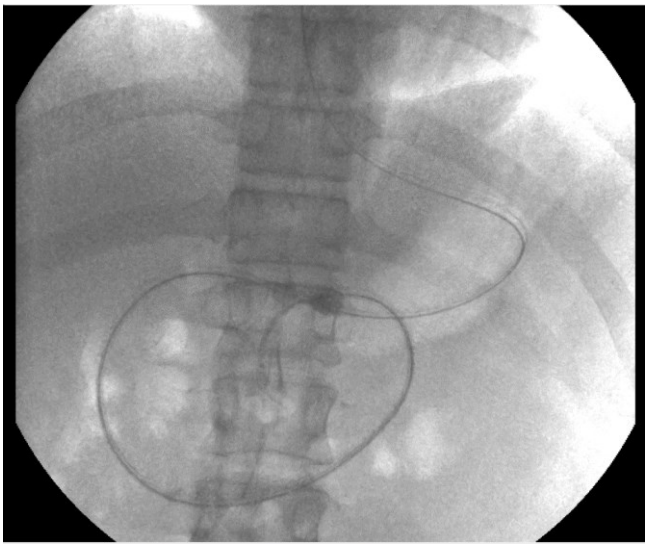


Volunteer # 6

Phase I

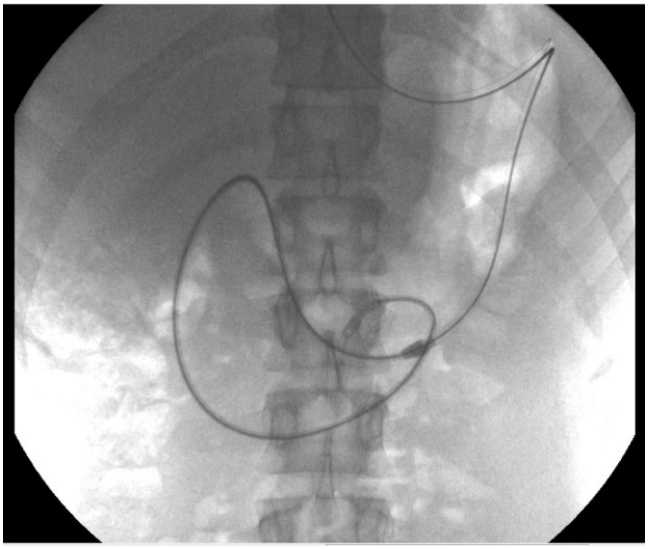


Phase II



Volunteer # 7

Phase I



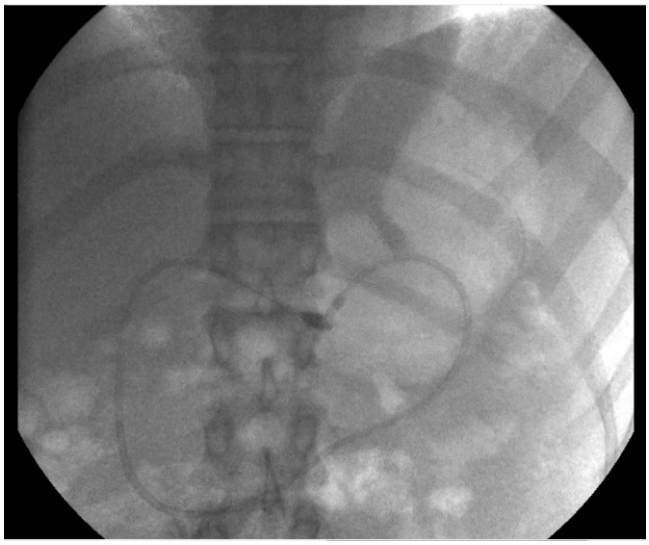
Voluntary withdrawal from the study after the meal was administered. The volunteer was feeling uncomfortable with the tube presence.

Volunteer # 8

Phase I

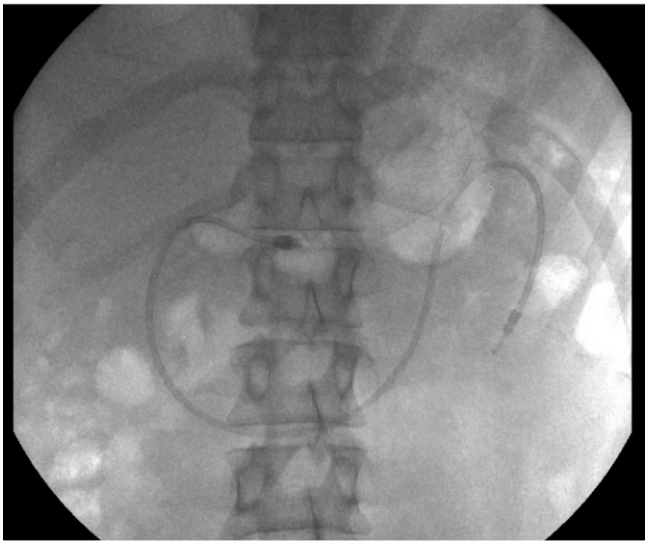
not available

Phase II

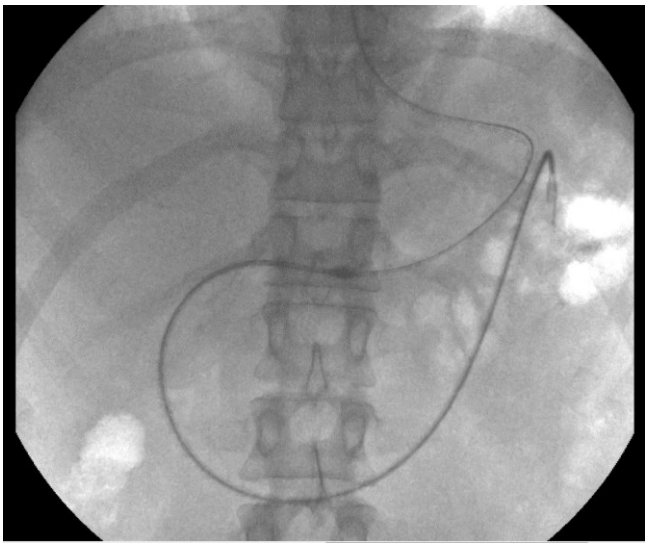


Volunteer # 9

Phase I

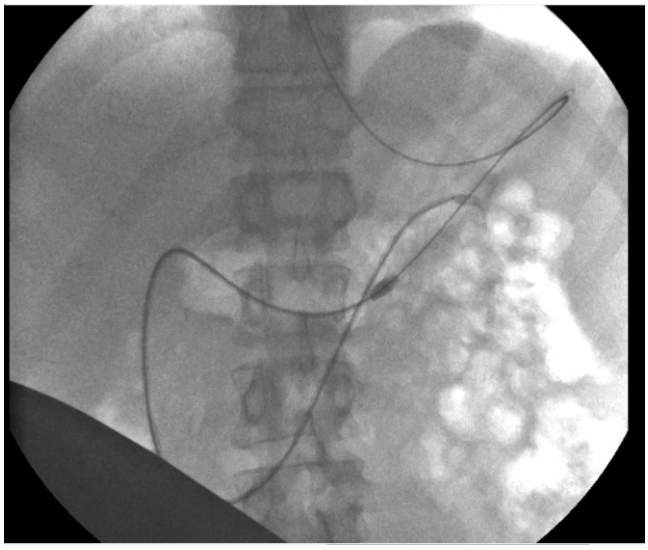


Phase II

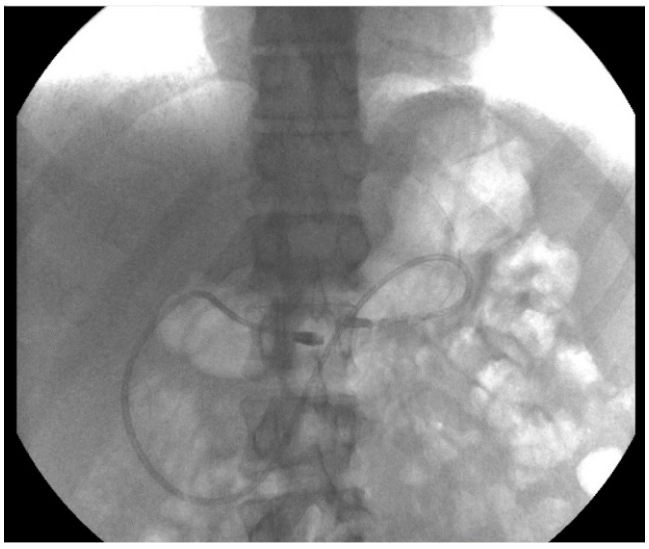


Volunteer # 10

Phase I



Phase II



APPENDIX III Analytical Methods for the determination of Active Pharmaceutical Ingredients and Physicochemical Parameters

Ap III.1 Paracetamol

For the determination of the concentration of paracetamol in samples of antral contents and contents of the upper small intestine and their respective aqueous and micellar phases a HPLC-UV gradient elution method is used, based on a published method (Vertzoni *et al*. 2003)(Vertzoni M. *et al*., 2003).

- Precolumn: BDS C18 (10 x 4.6 mm, 5 µm)
- Column: BDS C18 (250 x 4.6 mm, 5µm)
- Mobile Phase:

  Line A: aqueous buffer of KH2PO4 0.05 M containing 1% CH3COOH (pH 6.5) and methanol - 80 : 20 v/v

  Line B: Methanol
- Flow: 0.8 mL/min
- Wavelength: 242 nm
- Injection volume: 50 µL
- Gradient program:

Time (min)	% Line A	% Line B
0 - 9	100	0
9 - 13	30	70
13 - 17	30	70
17 - 21	100	0
21 - 28	100	0

- Sample treatment

  Protein precipitation is performed with $HClO_4$ 5%. The sample is then vortexed for at least 1 min and centrifuged (10 min, 10000 rpm, 10 °C). The intermediate aqueous phase is injected to the HPLC. Further dilution, if needed, is done with mobile phase.

- Calibration curves

  After confirming that the calibration curves in mobile phase, in gastric contents and in duodenal contents is of similar slope, it was decided to proceed with the analysis obtaining each experimental day's calibration curve in mobile phase.

  In Table Ap.III.1.1 the characteristics of calibration curves in mobile phase, in gastric contents and in duodenal contents are presented. In Figures Ap.III.1.1, Ap.III.1.2, Ap.III.1.3, typical chromatograms of a standard paracetamol solution in mobile phase, in gastric

contents and in duodenal contents are presented, whereas in Figures Ap.IIII.1.4 and Ap.IIII.1.5 chromatograms from the determination of paracetamol in samples of antral contents and contents of the upper small intestine (volunteer 10 - Phase II, 75 min and 60 min respectively) are presented.

Table Ap.III.1.1 Characteristics of calibration curves of paracetamol in mobile phase, in mobile phase, in gastric contents and in duodenal contents*

Calibration Curve	Medium	Concentration range (µg/mL)	Points	Slope ± SE	Intersection ± SE	R^2
# 1	mobile phase	0.125 - 0.750	6	4.588 ± 0.036	0.019 ± 0.017	0.999
# 2	gastric contents	0.125 - 0.750	6	4.358 ± 0.053	0.039 ± 0.026	0.999
# 3	duodenal contents	0.125 - 0.750	6	4.388 ± 0.079	0.017 ± 0.038	0.999
# 4	mobile phase	0.100 - 1.000	5	4.363 ± 0.026	0.021 ± 0.016	0.999
# 5	mobile phase	1.000 - 15.000	7	4.371 ± 0.012	0.20 ± 0.11	0.999

* LOQ: 100 ng/mL

Figure Ap.III.1.1: Typical chromatogram of a standard paracetamol solution (0.75 µg/mL) in mobile phase

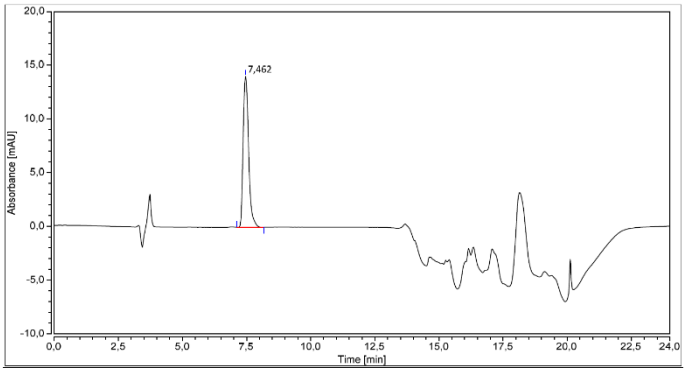


Figure Ap.III.1.2: Typical chromatogram of a standard paracetamol solution (0.75 µg/mL) in gastric contents

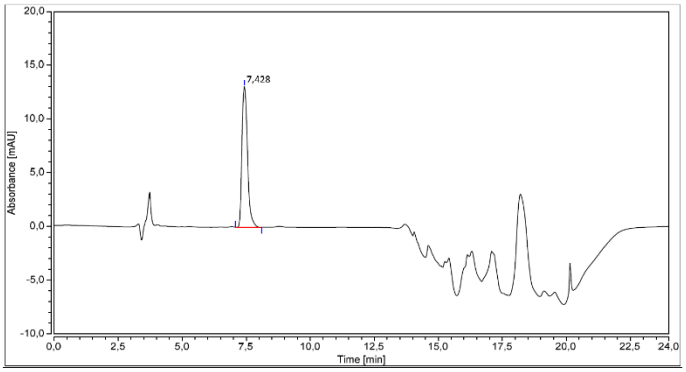


Figure Ap.III.1.3: Typical chromatogram of a standard paracetamol solution (0.75 µg/mL) in duodenal contents

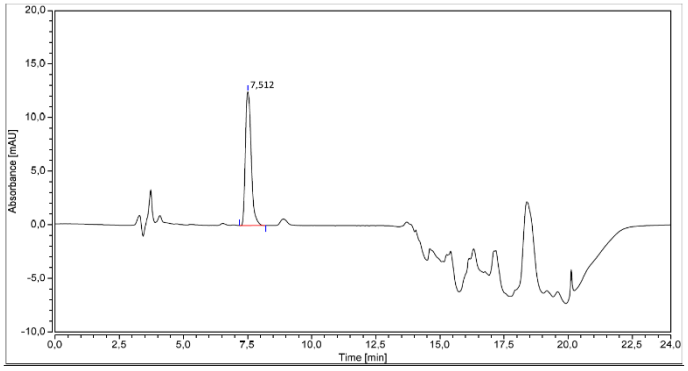


Figure Ap.III.1.4: Chromatogram of paracetamol in sample of antral contents

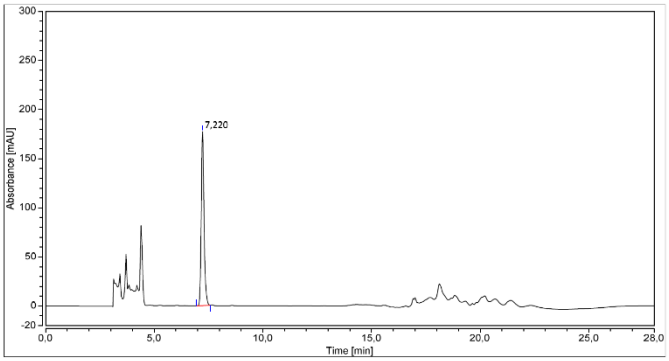
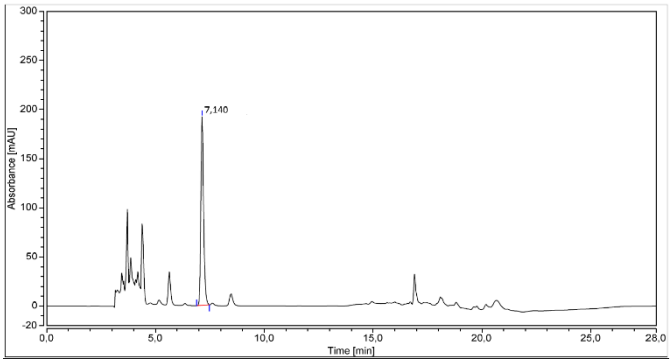


Figure Ap.III.1.5: Chromatogram of paracetamol in sample of contents of the upper small intestine



Ap III.2 Danazol

For the determination of the concentration of danazol in samples of antral contents and contents of the upper small intestine and their respective aqueous and micellar phases an HPLC-UV isocratic elution method is used, that is based on a published method (Vertzoni *et al*., 2012)

- Precolumn: BDS C18 (10 x 4.6 mm, 5 μm)
- Column: BDS C18 (150 x 3.0 mm, 5μm)
- Mobile Phase: Acetonitrile : Water - 70 : 30 v/v
- Flow: 0.5 mL/min
- Wavelength: 286 nm
- Injection volume: 50 μL
- Sample treatment

  Protein precipitation is performed with acetonitrile. The sample is then vortexed for at least 1 min and centrifuged (10 min, 4000 rpm, 10 °C). The supernatant is injected to the HPLC. Further dilution, if needed, is done with mobile phase.

- Calibration curves

  After confirming that the calibration curves in mobile phase, in gastric contents and in duodenal contents is of similar slope, it was decided to proceed with the analysis, obtaining each experimental day's calibration curve in mobile phase.

  In Table Ap.III.2.1 the characteristics of calibration curves in mobile phase, in gastric contents and in duodenal contents are presented. In Figures Ap.III.2.1, Ap.III.2.2, Ap.III.2.3, typical chromatograms of a standard danazol solution in mobile phase, in gastric contents and in duodenal contents are presented, whereas in Figures Ap.III.2.4 and Ap.III.2.5 chromatograms from the determination of danazol in samples of antral contents and contents of the upper small intestine (volunteer 10 - Phase I, 75 min and 120 min respectively) are presented.

Table Ap.III.2.1 Characteristics of calibration curves of danazol in mobile phase, in gastric contents and in duodenal contents *

Calibration Curve	Medium	Concentration range (µg/mL)	Points	Slope ± SE	Intersection ± SE	R^2
# 1	mobile phase	0.125 - 0.750	6	3.547 ± 0.060	-0.019 ± 0.029	0.999
# 2	gastric contents	0.125 - 0.750	6	3.531 ± 0.079	-0.029 ± 0.039	0.999
# 3	duodenal contents	0.125 - 0.750	6	3.554 ± 0.019	0.0297 ± 0.0093	0.999
# 4	mobile phase	0.005 - 0.1	6	3.504 ± 0.032	0.0023 ± 0.0018	0.999
# 5	mobile phase	0.1 - 10	9	3.531 ± 0.016	0.047 ± 0.071	0.999

* LOQ: 5 ng/mL

Figure Ap.III.2.1: Typical chromatogram of a standard danazol solution (0.50 µg/mL) in mobile phase

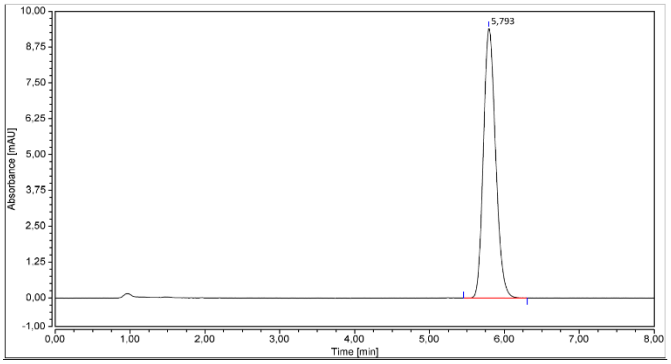


Figure Ap.III.2.2: Typical chromatogram of a standard danazol solution (0.50 µg/mL) in gastric contents

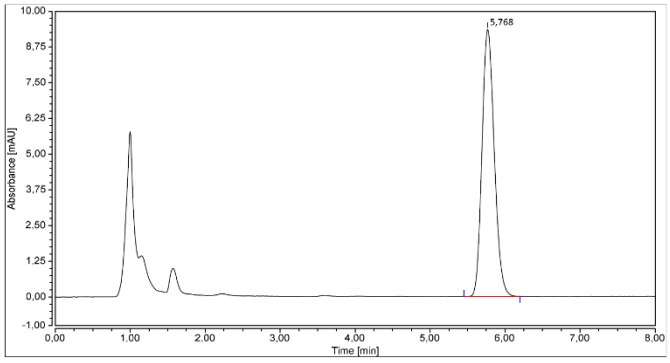


Figure Ap.III.2.3: Typical chromatogram of a standard danazol solution (0.50 µg/mL) in duodenal contents

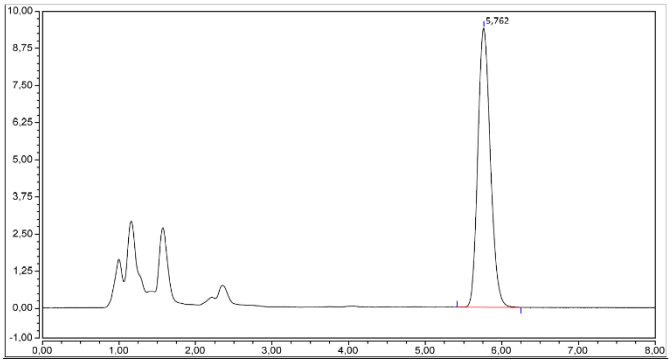


Figure Ap.III.2.4: Chromatogram of danazol in sample of antral contents

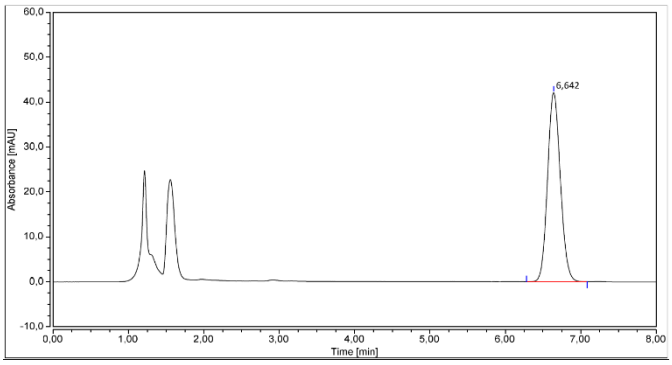
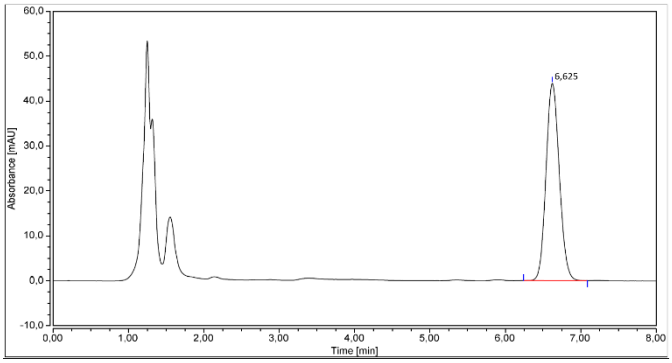


Figure Ap.III.2.5: Chromatogram of danazol in sample of contents of the upper small intestine



Ap III.3 Phenol Red

For the determination of the concentration of phenol red in samples of antral contents and contents of the upper small intestine and their respective aqueous and micellar phases an HPLC-UV-Vis isocratic elution method is used, that is based on a published method (Oberle *et al*., 1990)

- Precolumn: BDS C18 (10 x 4.6 mm, 5 µm)
- Column: BDS C18 (150 x 3.0 mm, 5µm)
- Mobile Phase: Aqueous phase : Methanol - 50 : 50 v/v

  The aqueous phase was prepared in a 1 l volumetric flask, adding 500 mL KH2PO4 0.1 M, 300 mL water, adjusting the pH to 3 with HPO3 and diluting to volume.
- Flow: 0.5 mL/min
- Wavelength: 423 nm
- Injection volume: 50 µL
- Sample treatment

  Protein precipitation is performed with $HClO_4$ 5%. The sample is then vortexed for at least 1 min and centrifuged (10 min, 10.000 rpm, 10 °C). The intermediate aqueous phase is injected to the HPLC. Further dilution, if needed, is done with $HClO_4$ 5%.

- Calibration curves

  After confirming that the calibration curves in perchloric acid, in gastric contents and in duodenal contents is of similar slope, it was decided to proceed with the analysis, obtaining each experimental day's calibration curve in perchloric acid.

  In Table Ap.III.3.1 the characteristics of calibration curves in perchloric acid, in gastric contents and in duodenal contents are presented. In Figures Ap.III.3.1, Ap.III.3.2, Ap.III.3.3, typical chromatograms of a standard phenol red solution in perchloric acid, in gastric contents and in duodenal contents are presented, whereas in Figures Ap.III.3.4 and Ap.III.3.5 chromatograms from the determination of phenol red in samples of antral contents and contents of the upper small intestine (volunteer 10 - Phase, 135 min and 150 min respectively) are presented.

Table Ap.III.3.1 Characteristics of calibration curves of phenol red in perchloric acid, in gastric contents and in duodenal contents *

Calibration Curve	Medium	Concentration range (µg/mL)	Points	Slope ± SE	Intersection ± SE	R^2
# 1	perchloric acid	0.05 - 2.00	8	4.788 ± 0.064	0.045 ± 0.064	0.999
# 2	gastric contents	0.05 - 2.00	8	4.851 ± 0.052	0.065 ± 0.052	0.999
# 3	duodenal contents	0.05 - 2.00	8	4.747 ± 0.09	0.092 ± 0.091	0.998
# 4	perchloric acid	0.05 - 2.00	9	4.909 ± 0.044	0.066 ± 0.042	0.999
# 5	perchloric acid	0.05 - 2.00	9	4.787 ± 0.039	-0.092 ± 0.037	0.999

* LOQ: 50 ng/mL

Figure Ap.III.3.1: Typical chromatogram of a standard phenol red solution (1 µg/mL) in perchloric acid

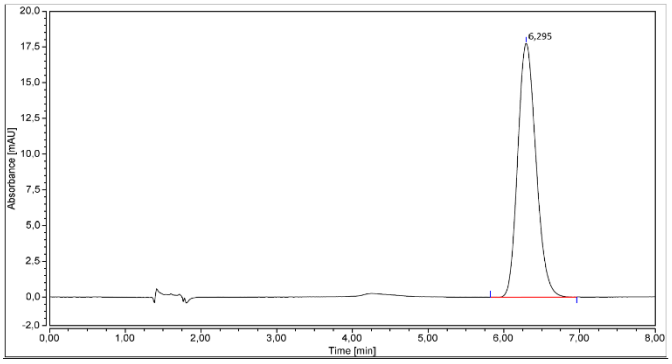


Figure Ap.III.3.2: Typical chromatogram of a standard phenol red solution (1 µg/mL) in gastric contents

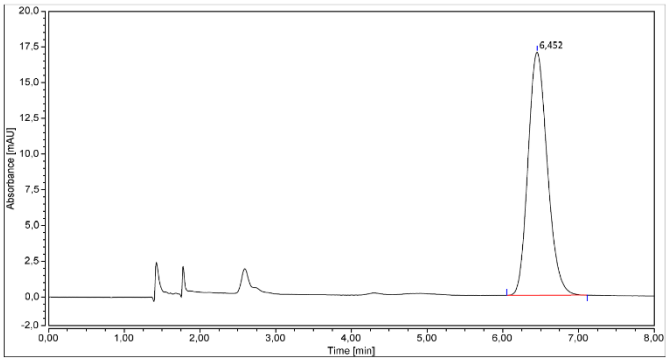


Figure Ap.III.3.3: Typical chromatogram of a standard phenol red solution (1 µg/mL) in duodenal contents

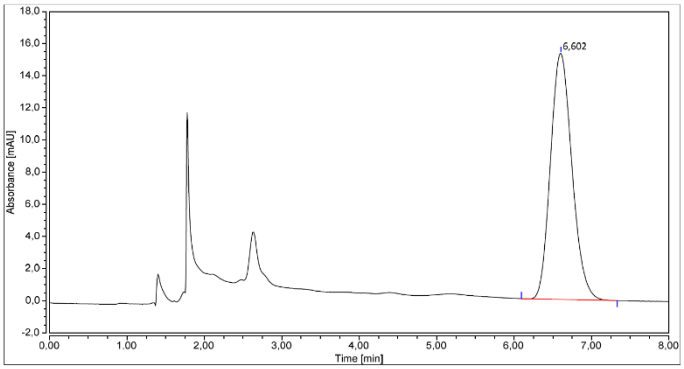


Figure Ap.III.3.4: Chromatogram of phenol red in sample of antral contents

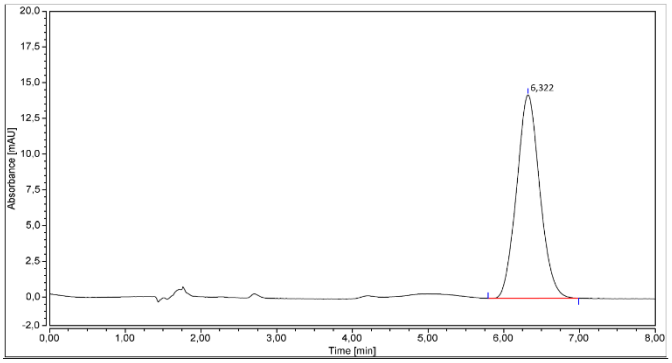
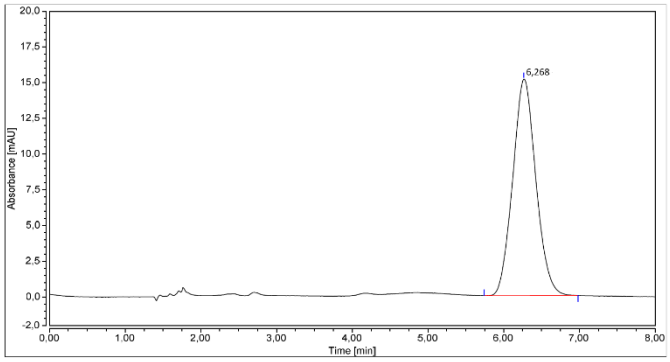


Figure Ap.III.3.5: Chromatogram of phenol red in sample of contents of the upper small intestine



Ap III.4 Bile acids

The concentrations of the following bile acids were determined in samples of contents of the upper small intestine and their respective micellar phases: taurocholic acid (TC), glycocholic acid (GC), taurochenodeoxycholic acid (TCDC), ursodeoxycholic acid (UDC), glycochenodeoxycholic acid (GCDC), cholic acid (C) and glycodeoxycholic acid (GDC). For the determination of the concentration of bile salts an HPLC isocratic elution method with a Charged Aerosol Detector was used, developed by (Vertzoni *et al*., 2008)

- Precolumn: BDS C18 (10 x 4.6 mm, 5 µm)
- Column: BDS C18 (250 x 4.6 mm, 5µm)
- Mobile Phase: Methanol : Aqueous phase - 67 : 33 v/v
  The aqueous phase is a buffer of ammonium formate 20 mM, formic acid 0.5% and triethylamine 0.2% (pH 3).
- Flow: 1.0 mL/min
- Injection volume: 50 µL
- Sample treatment
  Samples are treated with acetonitrile, vortexed for at least 1 min, centrifuged (10 min, 10000 rpm, 10 °C) and diluted with mobile phase before injected to the HPLC. Further or minor dilution is done accordingly, if needed.

- Calibration curves
  For each bile acid a stock solution of 10 mM concentration in methanol was prepared. Next, two mixed stock solutions, containing all seven bile salts in 1 mM concentration in acetonitrile were prepared. Mixed standard solutions in mobile phase were prepared to obtain the calibration curves.

In the peak area values obtained for each bile acid, the curve $y = y_0 + ax + bx^2$ was fitted.
In Tables Ap.III.4.1 - Ap.III.4.7 the characteristics of calibration curves for each bile acid are presented.

In Figures Ap.III.4.1 a typical chromatogram of a standard mixed bile acid solution (100 µM) is presented, whereas in Figures Ap.III.4.2 and Ap.III.4.3 chromatograms from the determination of bile acids in samples of contents of the upper small intestine (volunteer 8, Phase II, 180 min) and in the micellar phase of contents of the upper small intestine (volunteer 9, Phase I, 120 min) are presented.

Table Ap.III.4.1 Characteristics of calibration curves of taurocholic acid (TC) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SE	a ± SE	b ± SE	R^2
# 1	mobile phase	5 - 300	7	-212754.794 ± 335462.349	122318.302 ± 7334.715	-81.740 ± 24.167	0.999
# 2	mobile phase	5 - 200	6	-90135.799 ± 167237.433	128389.179 ± 5213.522	-82.138 ± 24.665	0.999
# 3	mobile phase	10 - 300	6	-173171.205 ± 359317.348	124683.323 ± 7017.754	-92.059 ± 22.261	0.999

* LOQ: 5 µM

Table Ap.III.4.2 Characteristics of calibration curves of glycocholic acid (GC) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SE	a ± SE	b ± SE	R^2
# 1	mobile phase	5 - 400	8	-123243.762 ± 113532.147	124146.365 ± 1854.556	-97.815 ± 4.7031	0.999
# 2	mobile phase	5 - 500	9	-550907.566 ± 261708.634	127967.112 ± 3353.725	-65.653 ± 6.907	0.999
# 3	mobile phase	5 - 400	8	-175176.970 ± 173423.096	124721.075 ± 2832.880	-83.439 ± 7.184	0.999

* LOQ: 5 µM

Table Ap.III.4.3 Characteristics of calibration curves of taurochenodeoxycholic acid (TCDC) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SE	a ± SE	b ± SE	R^2
# 1	mobile phase	5 - 300	7	2387.563 ± 269518.473	127067.485 ± 5892.908	-40.869 ± 19.417	0.999
# 2	mobile phase	5 - 300	7	-372047.156 ± 324840.996	123797.408 ± 7102.482	-29.369 ± 23.402	0.999
# 3	mobile phase	5 - 300	7	-441928.275 ± 770139.671	126435.120 ± 16838.719	11.572 ± 55.482	0.996

* LOQ: 5 µM

Table Ap.III.4.4 Characteristics of calibration curves of ursodeoxycholic acid (UDC) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SE	a ± SE	b ± SE	R^2
# 1	mobile phase	5 - 300	7	-81450.903 ± 76120.939	116330.981 ± 1664.346	-71.329 ± 5.484	0.999
# 2	mobile phase	5 - 300	7	-62585.884 ± 77588.616	116356.260 ± 1696.435	-77.411 ± 5.590	0.999
# 3	mobile phase	5 - 300	7	7993.982 ± 164111.277	117671.997 ± 3588.208	-65.334 ± 11.823	0.996

* LOQ: 5 µM

Table Ap.III.4.5 Characteristics of calibration curves of glycochenodeoxycholic acid (GCDC) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SE	a ± SE	b ± SE	R^2
# 1	mobile phase	5 - 500	9	-612539.144 ± 459376.976	121058.504 ± 5886.790	-50.708 ± 12.123	0.998
# 2	mobile phase	5 - 500	8	-212071.805 ± 378918.364	121269.042 ± 4476.594	-60.398 ± 9.093	0.999
# 3	mobile phase	5 - 500	9	-106427.910 ± 266380.457	121107.440 ± 3413.592	-71.222 ± 7.030	0.999

* LOQ: 5 µM

Table Ap.III.4.6 Characteristics of calibration curves of cholic acid (C) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SE	a ± SE	b ± SE	R^2
# 1	mobile phase	5 - 400	8	-668312.042 ± 297880.339	124714.777 ± 4865.897	1.059 ± 12.340	0.999
# 2	mobile phase	5 - 300	7	-432740.216 ± 199532.022	124646.989 ± 4362.666	-20.453 ± 14.375	0.999
# 3	mobile phase	5 - 300	7	-132068.958 ± 65837.326	120243.392 ± 1439.500	19.926 ± 4.743	1

* LOQ: 5 µM

Table Ap.III.4.7 Characteristics of calibration curves of glycodeoxycholic acid (GDC) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SE	a ± SE	b ± SE	R^2
# 1	mobile phase	5 - 400	8	-648511.282 ± 420090.035	122106.682 ± 6862.204	-16.918 ± 17.402	0.999
# 2	mobile phase	5 - 300	7	-278513.905 ± 188473.479	123396.346 ± 4120.877	-48.073 ± 13.578	0.999
# 3	mobile phase	5 - 300	7	-187108.608 ± 175315.892	121060.360 ± 3833.193	-7.518 ± 12.630	0.999

* LOQ: 5 µM

Note: cholic acid (C) was not present in samples collected from the upper small intestine

Figure Ap.III.4.1: Typical chromatogram of a mixed standard solution of bile acids in mobile phase. The concentration of each bile acid was 100 µM. From left to right, the numbers indicate the retention times of TC, GC, TCDC, UDC, GCDC, C, and GDC.

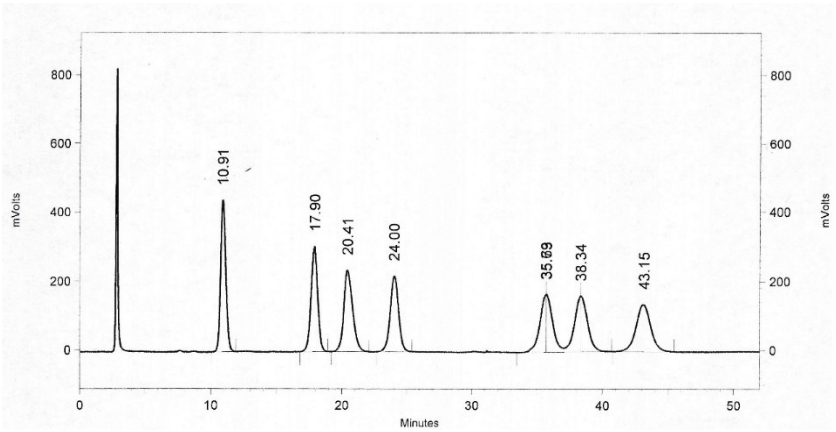


Figure Ap.III.4.2: Chromatogram of bile acids in sample of contents of the upper small intestine. From left to right, the numbers indicate the retention times of TC, GC, TCDC, UDC, GCDC, C, and GDC. No C was detected.

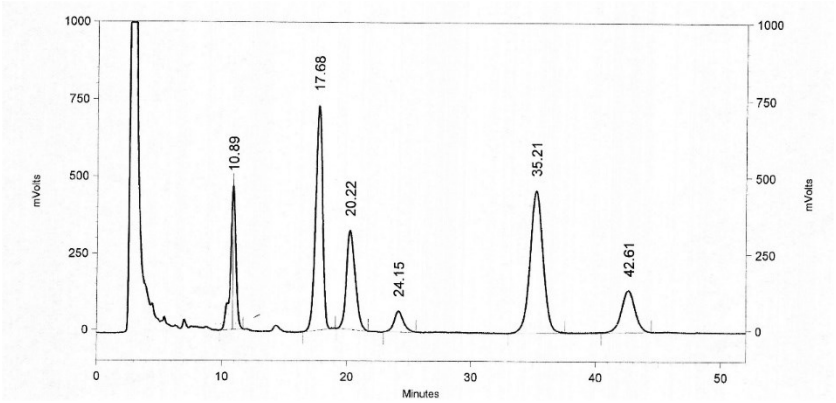
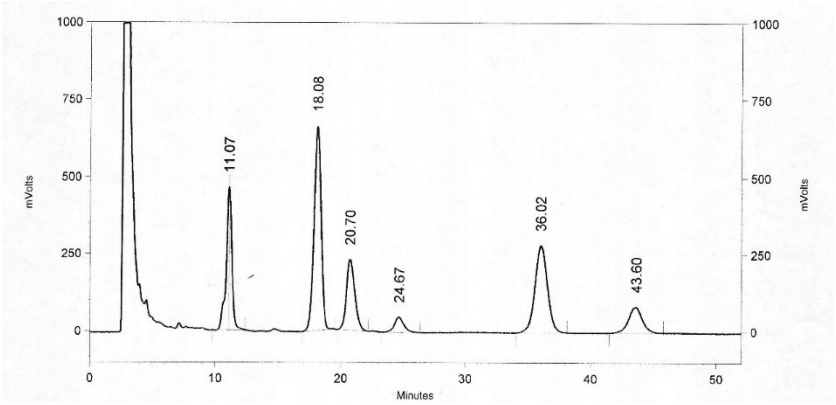


Figure Ap.III.4.3: Chromatogram of bile acids in the micellar phase of contents of the upper small intestine. From left to right, the numbers indicate the retention times of TC, GC, TCDC, UDC, GCDC, C, and GDC. No C was detected.



During bile acids' analysis of samples collected in TIM-1 experiments (i.e.: 100% bile solution samples, samples from the duodenal compartment of TIM-1 model and their respective micellar phases and samples from the jejunal compartment of TIM-1 model their respective micellar phases) a different set of individual bile acids was identified. Porcine bile was found to not contain GC, UDC, and GDC in contrast to the human samples, but contained another two bile acids instead: glycohyodeoxycholic acid (GHDC) and glycohyocholic acid (GHC).

In Figure Ap.III.4.4 a typical chromatogram of a standard mixed bile acid solution (100 µM) is presented, whereas in Figure Ap.III.4.5 a chromatogram from the determination of bile acids in the 100% porcine bile solution used in TIM-1 experiments is presented.

Figure Ap.III.4.4: Typical chromatogram of a mixed standard solution of bile acids in mobile phase. The concentration of each bile acid was 100 µM. From left to right, the numbers indicate the retention times of GHC, TC, GHDC, GC, TCDC, UDC, GCDC, and GDC.

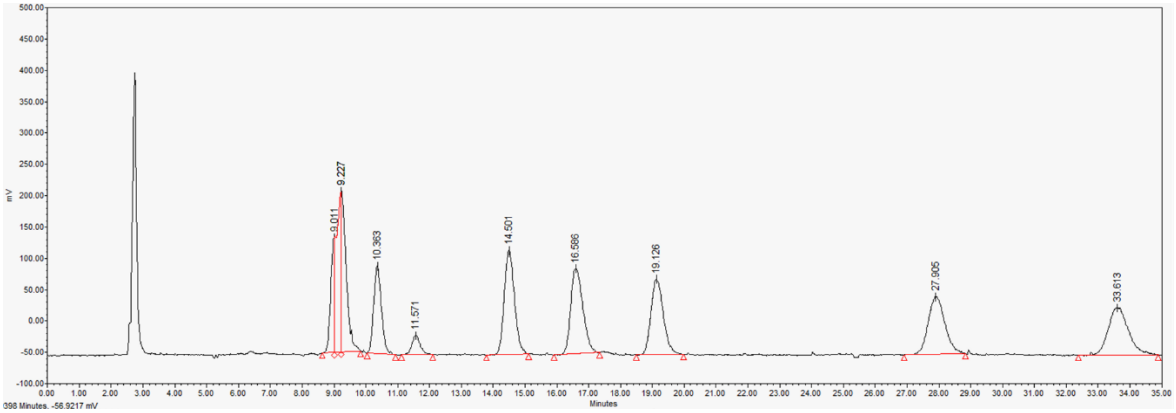
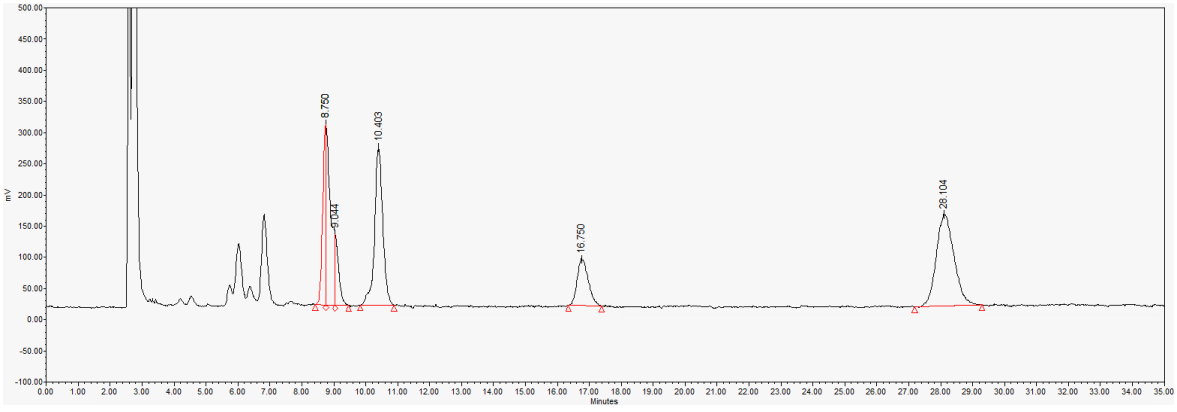


Figure Ap.III.4.5: Chromatogram of bile acids in a 100% bile solution sample used in TIM-1 experiments. From left to right, the numbers indicate the retention times of GHC, TC, GHDC, TCDC, and GCDC. No GC, UDC, and GDC were detected in porcine bile.



Ap III.5 Phospholipids, neutral lipids and fatty acids

The concentrations of the following lipids and fatty acids were determined in samples of antral contents and contents of the upper small intestine and their respective aqueous and micellar phases: 3-sn-lysophosphatidylcholine (Lyso-PC), phosphatidylcholine from egg yolk (egg-PC), linoleic acid (LA), oleic acid (OA), stearic acid (SA), 1-monooleylrac-glycerol (MG), cholesterol (CHO), dipalmitin (DG-P), 1,2-dioleyl-rac-glycerol (DG-O), dipalmitin (DG-P), glyceryl trioleate, glyceryl trilinoleate.

For the determination of the concentration of lipids an HPLC gradient elution method with a Charged Aerosol Detector was used, developed by Diakidou *et al* (Diakidou *et al*., 2009)

- Precolumn: BDS C18 (10 x 4.6 mm, 5 µm)
- Column: BDS C18 (250 x 4.6 mm, 5µm)
- Mobile Phase:

Line A: Methanol : Acetonitrile : Aqueous phase - 65 : 25 : 10 v/v/v) : Isopropanol - 96 : 4 v/v

The aqueous phase is a buffer of ammonium formate 20 mM, formic acid 0.5% and triethylamine 0.2% (pH 3).

Line B: Isopropanol

- Flow: 0.5 mL/min
- Injection volume: 50 µL
- Gradient program:

Time (min)	% Line A	% Line B
0	100	0
30	100	0
32	50	50
52	50	50
57	30	70
100	0	100
110	100	0
120	100	0

- Sample treatment

Samples are treated with isopropanol, vortexed for at least 1 min, centrifuged (10 min, 10.000 rpm, 10 °C) and diluted with mobile phase before injected to the HPLC. Further or minor dilution is done accordingly, if needed.

- Calibration curves

For LA, OA and MG an individual stock solution of 10 mM concentration in acetonitrile was prepared. For Lyso-PC, egg-PC, SA, CHO, DG(P), DG(O) glyceryl trioleate and glyceryl trilinoleate, an individual stock solution in isopropanol was prepared.

Next, a mixed stock solution containing LA, OA, SA, MG, Lyso-PC, CHO, DG(P), DG(O), and glyceryl trioleate in 1 mM concentrations each was prepared in propanol. Mixed standard solutions in mobile phase were prepared to obtain the calibration curves.

Glyceryl trilinoleate was added later in the analysis, with separate calibration curves, after observing many different peaks in the area of triglycerides in the samples. A standard of glyceryl tripalmitate was also tested but not identified in the samples (peak at 80 min).

Calibration curves were separate for egg-PC as well. Determination of egg-PC was performed after integrating the sum of peaks in the area between 45-58 min and subtracting the area of the peak corresponding to cholesterol (56.97 min).

In the peak area values obtained for each lipid or fatty acid, the curve $y = y_0 + ax + bx^2$ was fitted. In Tables Ap.III.5.1 - Ap.III.5.11 the characteristics of calibration curves for each lipid are presented.

In Figures Ap.III.5.1, Ap.III.5.2, Ap.III.5.3, typical chromatograms of standard lipid and fatty acids solutions are presented, whereas in Figures Ap.III.5.4 - Ap.III.5.7 chromatograms from the determination of lipids and fatty acids in samples of antral contents, contents of the upper small intestine, the aqueous phase of antral contents, and the micellar phase of contents of the upper small intestine (volunteer 2 - Phase I, 135 min / volunteer 1 - Phase I, 75 min / volunteer 8 - Phase II, 90 min / volunteer 6 - Phase I, 60 min, respectively) are presented.

Table Ap.III.5.1 Characteristics of calibration curves of 3-sn-lysophosphatidylcholine (Lyso-PC) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SD	a ± SD	b ± SD	R^2
# 1	mobile phase	10 - 80	4	-315392.000 ± 701559.774	496197.236 ± 41610.509	-1417.513 ± 440.726	0.999
# 2	mobile phase	5 - 40	4	-461362.167 ± 271572.131	498565.662 ± 32214.661	-1312.196 ± 682.416	0.999
# 3	mobile phase	10 - 100	4	-581546.547 ± 802009.980	496047.887 ± 35836.166	-1195.693 ± 322.0159	0.999

* LOQ: 5 µM

Table Ap.III.5.2 Characteristics of calibration curves of linoleic acid (LA) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SD	a ± SD	b ± SD	R^2
# 1	mobile phase	1 - 100	7	31723.381 ± 49601.284	128960.044 ± 3240.632	-145.906 ± 32.356	0.999
# 2	mobile phase	10 - 100	4	-114122.564 ± 190679.285	120585.545 ± 8520.112	-325.191 ± 76.560	0.999
# 3	mobile phase	10 - 80	4	-687740.332 ± 319197.274	129591.333 ± 18932.044	-328.326 ± 200.523	0.999

* LOQ: 1 µM

Table Ap.III.5.3 Characteristics of calibration curves of Oleic acid (OA) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SD	a ± SD	b ± SD	R^2
# 1	mobile phase	10 - 100	4	73213.357 ± 323171.312	123517.611 ± 14440.241	-133.040 ± 129.757	0.999
# 2	mobile phase	10 - 80	4	17004.334 ± 164075.463	123430.320 ± 9731.548	-99.516 ± 103.074	0.999
# 3	mobile phase	5 - 60	4	41404.416 ± 112147.989	126934.238 ± 9175.268	-105.652 ± 133.236	0.999

* LOQ: 5 µM

Table Ap.III.5.4 Characteristics of calibration curves of stearic acid (SA) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SD	a ± SD	b ± SD	R^2
# 1	mobile phase	1 - 40	5	49902.163 ± 107042.542	134507.973 ± 15117.654	143.724 ± 348.515	0.999
# 2	mobile phase	5 - 30	4	193854.503 ± 92890.062	131439.917 ± 13089.911	586.438 ± 353.238	0.999
# 3	mobile phase	1 - 20	4	58394.998 ± 75537.554	134692.364 ± 18925.014	1626.218 ± 844.444	0.999

* LOQ: 1 µM

Table Ap.III.5.5 Characteristics of calibration curves of 1-monooleylrac-glycerol (MG) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SD	a ± SD	b ± SD	R^2
# 1	mobile phase	10 - 100	4	-140595.962 ± 69555.281	192759.274 ± 3107.936	-279.503 ± 27.927	1
# 2	mobile phase	1 - 80	6	-33087.431 ± 66539.039	190259.719 ± 5275.915	-294.227 ± 62.774	0.999
# 3	mobile phase	1 - 80	6	-80612.959 ± 96401.750	195872.056 ± 7643.745	-290.302 ± 90.947	0.999

* LOQ: 1 µM

Table Ap.III.5.6 Characteristics of calibration curves of cholesterol (CHO) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SD	a ± SD	b ± SD	R^2
# 1	mobile phase	1 - 60	4	-73728.105 ± 242355.384	277708.388 ± 20477.204	-218.505 ± 312.393	0.999
# 2	mobile phase	5 - 60	4	-79149.838 ± 40043.138	278090.751 ± 3276.086	-338.465 ± 47.573	1
# 3	mobile phase	1 - 100	7	51267.757 ± 136332.367	274916.087 ± 8907.086	-240.820 ± 88.932	0.999

* LOQ: 1 µM

Table Ap.III.5.7 Characteristics of calibration curves of dipalmitin (DG-P) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SD	a ± SD	b ± SD	R^2
# 1	mobile phase	5 - 60	4	-468471.848 ± 352540.602	494385.782 ± 28842.725	-912.918 ± 418.830	0.999
# 2	mobile phase	5 - 60	4	-195992.483 ± 41241.291	498386.902 ± 3374.111	-1336.893 ± 48.996	1
# 3	mobile phase	10 - 80	4	-601447.825 ± 363160.599	497090.364 ± 21539.573	-1313.325 ± 228.141	0.999

* LOQ: 5 µM

Table Ap.III.5.8 Characteristics of calibration curves of 1,2-dioleyl-rac-glycerol (DG-O) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SD	a ± SD	b ± SD	R^2
# 1	mobile phase	10 - 80	4	-208697.500 ± 597108.178	506160.591 ± 35415.335	-1647.469 ± 375.109	0.999
# 2	mobile phase	1 - 50	6	-326016.772 ± 273217.113	506812.655 ± 29337.587	-2004.405 ± 557.489	0.999
# 3	mobile phase	5 - 60	4	-516054.700 ± 219534.384	506708.373 ± 17960.965	-2007.910 ± 260.814	0.999

* LOQ: 1 µM

Table Ap.III.5.9 Characteristics of calibration curves of egg-phosphatidyl-choline (egg-PC) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SD	a ± SD	b ± SD	R^2
# 1	mobile phase	5 - 120	5	929098.957 ± 1012504.438	541190.860 ± 51048.481	23.849 ± 409.467	0.999
# 2	mobile phase	5 - 150	8	1035879.191 ± 202154.555	540212.289 ± 7510.865	-84.465 ± 49.647	0.999
# 3	mobile phase	5 - 180	9	1118086.009 ± 294386.394	538456.842 ± 8819.042	-48.615 ± 49.172	0.999

* LOQ: 5 µM

Table Ap.III.5.10 Characteristics of calibration curves of glyceryl trilinoleate (TG-L) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SD	a ± SD	b ± SD	R^2
# 1	mobile phase	1 - 40	5	55444.232 ± 234100.623	612191.155 ± 33062.107	-3041.351 ± 762.198	0.999
# 2	mobile phase	1 - 40	4	-126691.667 ± 94816.548	594031.073 ± 11247.407	-2883.078 ± 238.258	1
# 3	mobile phase	1 - 40	5	-53972.808 ± 172569.609	602670.496 ± 24372.070	-3173.700 ± 561.862	0.999

* LOQ: 1 µM

Table Ap.III.5.11 Characteristics of calibration curves of glyceryl trioleate (TG-O) in mobile phase *

Calibration Curve	Medium	Concentration range (µM)	Points	y_0 ± SD	a ± SD	b ± SD	R^2
# 1	mobile phase	1 - 40	5	172886.394 ± 157483.374	643830.622 ± 22241.427	-2084.328 ± 512.743	0.999
# 2	mobile phase	1 - 20	4	261738.647 ± 112674.216	647137.181 ± 28229.153	-631.401 ± 1259.600	0.999
# 3	mobile phase	5 - 60	4	97954.981 ± 19477.069	640270.645 ± 4879.744	864.412 ± 217.737	1

* LOQ: 1 µM

Figure Ap.III.5.1: Typical chromatogram of a mixed standard solution of lipids and fatty acids in mobile phase. The concentration of each lipid species was 40 µM. Retention times were approximately (19.12 and 33.62), 23.17, 26.07, 34.93, 42.58, 56.97, (58.54 and 59.70), (61.25 and 62.77), and 79.01 min for Lyso-PC, LA, MG, OA, SA, CHO, DG(O), DG(P), and TG, respectively.

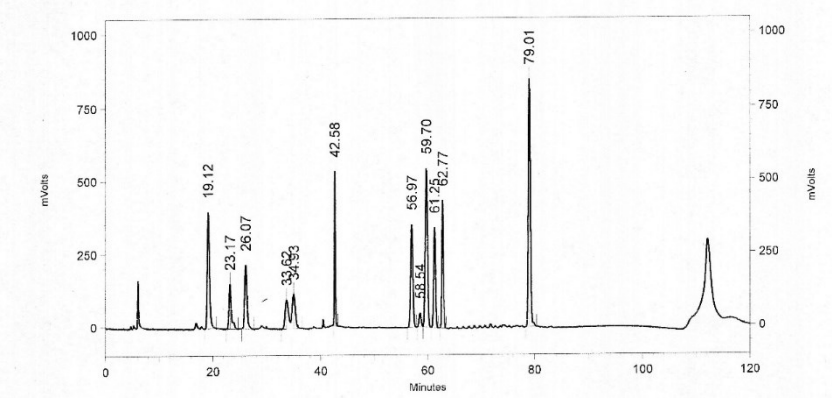


Figure Ap.III.5.2: Typical chromatogram of a standard solution of glyceryl trilinoleate (30 µM) in mobile phase. Retention time was 70.23 min.

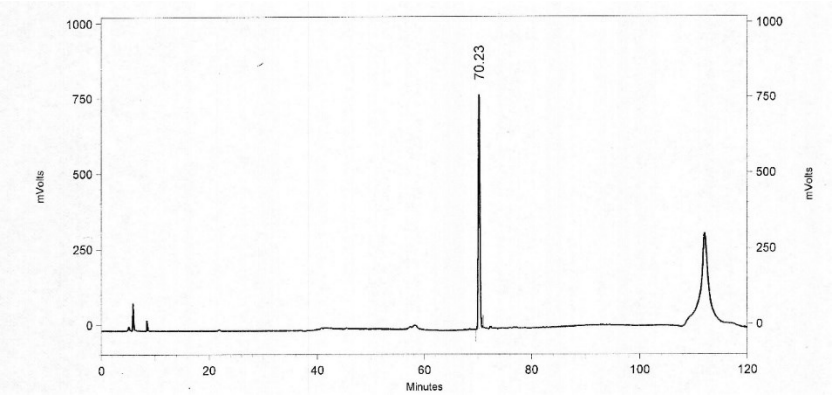


Figure Ap.III.5.3: Typical chromatogram of a standard solution of egg-PC (100 µM) in mobile phase. Retention time was 45.0 - 58.0 min.

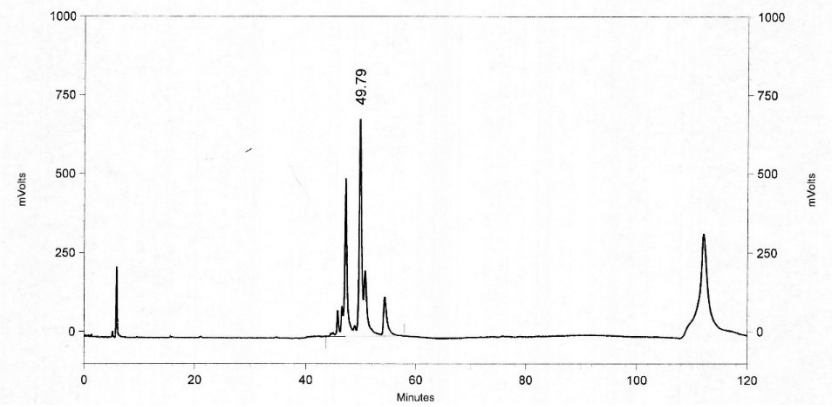


Figure Ap.III.5.4: Chromatogram of lipid species in sample of antral contents

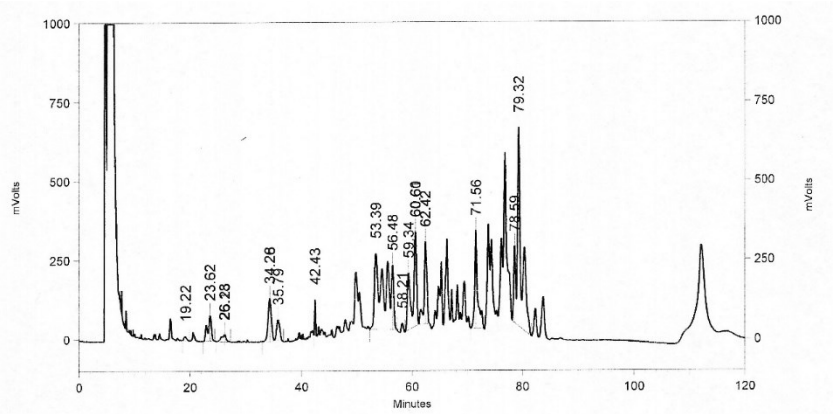


Figure Ap.III.5.5: Chromatogram of lipid species in the aqueous phase of antral contents

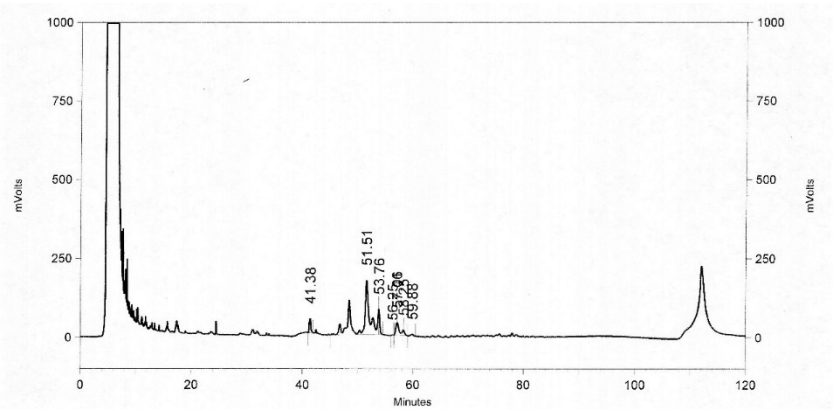


Figure Ap.III.5.6: Chromatogram of lipid species in sample of contents of the upper small intestine

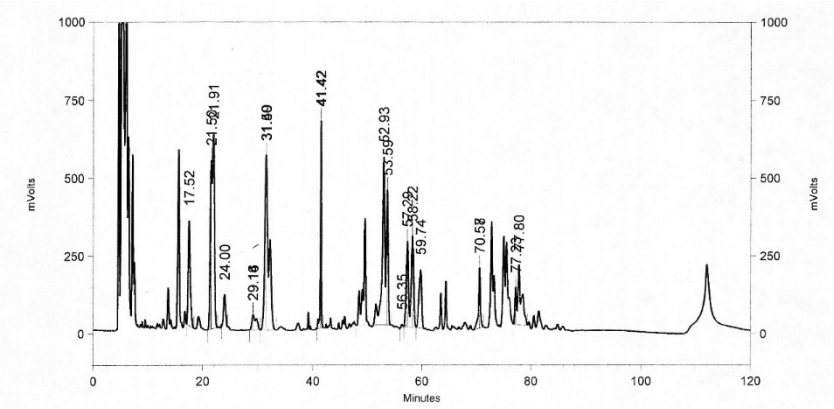
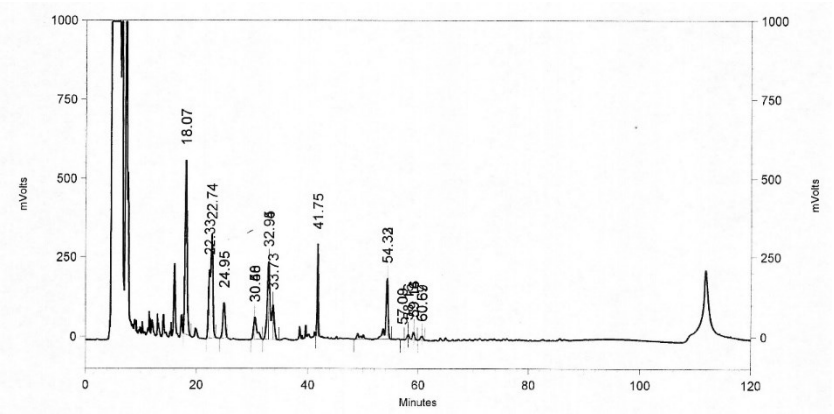


Figure Ap.III.5.7: Chromatogram of lipid species in the micellar phase of contents of the upper small intestine



Ap III.6 Osmolality

Osmolality describes the concentration of osmotically active particles in a solution. A liquid's osmolality is equal to the osmolality of all the dissolved particles in it. Osmotic pressure depends on the number of osmoles of solute per volume or mass unit and refers to the total solution, this is why it is measured per kilogram of water.

Osmolality was measured based on the depression of the sample's freezing point. 150 μL sample are put into the cooling cavity inside a glass measuring vessel. The sample is cooled at -16 °C and then, with a metallic needle dipped into the sample, called thermistor or temperature sensor, the sample is progressively crystallized. Crystallization leads to temperature increase; however, the final sample temperature is always lower than 0 °C. The difference between the final sample temperature from 0 °C is directly proportional to the number of free particles in the solution.

The aqueous phase of the gastric samples and the micellar phase of small intestinal samples were measured, to compare with the osmolality of media simulating the postprandial gastric and upper intestinal environment.

Each measurement was performed one time. The osmolality of the lipase inhibitors cocktail (Hernell *et al.*, 1990) was also measured and found to be 427 mOsm/kg. This value was subtracted from all sample measurements.

Ap III.7 pH and Buffer Capacity

Immediately upon aspiration, 1 mL of the collected sample is transferred in a plastic tube and their pH is measured.

The buffer capacity of samples aspirated from the antrum of the stomach was determined with titration with NaOH 0.1 N solution, whereas the buffer capacity of samples aspirated from the small intestine was determined with titration with HCl 0.1 N, until reaching a pH change of 1 unit to the increasing or decreasing direction, respectively.

The exact value was calculated with the following equation:

$$Buffer\ capacity\ (mmol/l/\Delta pH) = \frac{V_{acid/base} * C}{V_{sample}} * 1000$$

V_{sample} is the volume of the sample, i.e. 1 mL

$V_{acid/base}$ is the volume of NaOH or HCl solution required to change the pH of the sample by 1 pH unit

C is the molarity of the NaOH or HCl solution, i.e. 0.1 M

Each measurement was performed one time, in the hospital, immediately after aspiration of the sample.

Ap III.8 Particle size distribution

For the determination of the particle size distribution of the chewed versus homogenized meals, the following methodology was followed:

The total volume of the meal was initially measured. The meal was then let to pass sequentially through a 2 mm mesh diameter and a 1 mm mesh diameter sieve. The volume of meal with particles larger than 2 mm, between 1 and 2 mm, and less than 1 mm was measured.

For particles smaller than 1 mm the particle size analyzer a Malvern Mastersizer S (Malvern Panalytical Ltd, UK) was used. 100 µL sample were introduced in the sample cell (stirred cell) where it is dispersed in distilled water. The mixture is kept in suspension by rotating the stirrer bead within the cell at a rate of 2000 rpm, at room temperature. The size range 0.05 to 880 µm - 300RF lens was used. The volume-weighted relative and cumulative distribution of particles was measured, using the median particle diameter d[0.5] and the larger diameter of the 90% of smallest particles d[0.9].

Ap III.9 Viscosity

Viscosity was measured using the rotational viscometer RM 100 CP 2000 PLUS (LAMY Rheology, France) and the measuring cone and plate system MK-CP4005. A sample volume of 146 µL was placed on the viscometer's plate and the measuring cone was lowered in measuring position. The software VISCO-RM Soft was used to control the instrument. Each measurement was performed at ascending shear rates of 50 s^{-1}, 100 s^{-1} and 200 s^{-1}. The duration for each step was set at 10 s. Meal samples' viscosity was measured at two different temperatures: 25°C and 37°C, whereas luminal samples' viscosity was measured at 37°C. Each sample was measured in triplicate.

APPENDIX IV Physicochemical characteristics of the standard meal

Table Ap.IV.1 Physicochemical characteristics of the homogenized standard meal (n=3 meal preparations)

Parameter	**1**	**2**	**3**	**Mean (SD)**
Volume (mL)	532	534	530	532.0 (1.6)
Mass (g)	543.4	543.3	542.6	543.13 (0.35)
Density (kg/m^3)	1.022	1.017	1.024	1.0209 (0.0026)
pH	6.6	6.6	6.7	median 6.6
Buffer capacity (mmol/L/ΔpH)	29.3	27.4	23.7	26.8 (2.3)
Osmolality (total meal) (mOsm/kg)	433	438	444	438.0 (4.5)
Osmolality (supernatant after ultracentrifugation) (mOsm/kg)	417	430	422	423 (5.4)
Surface tension (supernatant after ultracentrifugation) (mN/m)	43.1	44.6	43.3	43.66 (0.86)

Table Ap.IV.2 Viscosity of the homogenized vs. chewed standard meal (n=3 meal preparations)

* Presented values are the mean of 3 measurements for each sample.

		Chewed meals			
Temperature	**Shear rate (s^{-1})**	**1**	**2**	**3**	**Mean (SD)**
25 ° C	**50**	1144.4	3395.3	1143.3	1894 (1300)
	100	1268.5	2640.8	1263.2	1724 (794)
	200	911.0	1321.4	767.9	1000 (287)
37 ° C	**50**	1798.9	2752.4	1033.1	1861 (861)
	100	1662.7	2234.3	1045.8	1648 (594)
	200	903.9	1058.9	667.4	877 (197)

		Chewed and then Homogenized meals			
Temperature	**Shear rate (s^{-1})**	**1**	**2**	**3**	**Mean (SD)**
25 ° C	**50**	2125.4	1758.2	1699.3	1861 (231)
	100	1990.1	1949.0	1680.9	1873 (168)
	200	1096.8	1056.7	937.2	1030 (83)
37 ° C	**50**	2083.1	2793.8	1824.1	2234 (502)
	100	1977.7	2550.3	1749.3	2092 (413)
	200	1089.2	1276.8	986.5	1118 (147)

		Homogenized meals			
Temperature	**Shear rate (s^{-1})**	**1**	**2**	**3**	**Mean (SD)**
25 ° C	**50**	1969.1	1521.6	1701.3	1731 (225)
	100	1834.5	1378.0	1602.8	1605 (228)
	200	1043.4	830.6	960.1	945 (107)
37 ° C	**50**	1798.4	1641.1	1747.3	1729 (80)
	100	1773.5	1495.8	1477.1	1582 (166)
	200	1009.8	885.0	918.2	938 (65)

APPENDIX V Particle size distribution data of the chewed vs the homogenized meal

Table Ap.V.1 Volume and particle size distribution on a volume basis for the standard meal (containing in addition 50 mL aqueous phenol red solution) after chewing and after homogenization.

	Chewed meals							
	Volume (mL)				**% total**			
	1	**2**	**3**	**Mean (SD)**	**1**	**2**	**3**	**Mean (SD)**
Total	650	545	670	622 (67)	(100)	(100)	(100)	(100)
> 2 mm	185	120	160	155 (33)	28.5	22.0	23.9	24.8 (3.3)
1 mm - 2 mm	95	70	105	90 (18)	14.6	12.8	15.7	14.4 (1.5)
< 1 mm	370	355	405	377 (26)	56.9	65.1	60.4	60.8 (4.1)

	Homogenized meals							
	Volume (mL)				**% total**			
	1	**2**	**3**	**Mean (SD)**	**1**	**2**	**3**	**Mean (SD)**
Total	532	534	530	532.0 (2.0)	(100)	(100)	(100)	(100)
> 2 mm	63	51	41	52 (11)	11.9	9.5	7.7	9.7 (2.1)
1 mm - 2 mm	70	51	88	70 (19)	13.1	9.5	16.7	13.1 (3.6)
< 1 mm	399	432	401	411 (19)	75.0	80.9	75.6	77.2 (3.3)

For particles smaller than 1 mm, particle size distribution was measured with Malvern Mastersizer S. Data are presented in the following tables.

Table Ap.V.2 Data on particle size distribution of #1 chewed standard meal

Particle size (μm)	1st measurement		2nd measurement		3rd measurement		Mean (SD)	
	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)
0,06	0,00	0,00	0,00	0,00	0,00	0,00	0 (0)	0 (0)
0,07	0,00	0,00	0,00	0,00	0,00	0,00	0 (0)	0 (0)
0,08	0,00	0,00	0,00	0,00	0,00	0,00	0 (0)	0 (0)
0,09	0,00	0,00	0,00	0,00	0,00	0,00	0 (0)	0 (0)
0,11	0,00	0,00	0,00	0,00	0,00	0,00	0 (0)	0 (0)
0,13	0,00	0,00	0,00	0,00	0,00	0,00	0 (0)	0 (0)
0,15	0,00	0,00	0,00	0,00	0,00	0,00	0 (0)	0 (0)
0,17	0,00	0,00	0,00	0,00	0,00	0,00	0,0009 (0,0016)	0 (0)
0,20	0,00	0,00	0,00	0,00	0,02	0,01	0,0060 (0,0095)	0,0023 (0,0031)
0,23	0,00	0,00	0,01	0,02	0,05	0,05	0,023 (0,026)	0,024 (0,022)
0,27	0,03	0,04	0,04	0,08	0,10	0,13	0,059 (0,036)	0,085 (0,049)
0,31	0,09	0,12	0,08	0,21	0,16	0,29	0,111 (0,044)	0,206 (0,082)
0,36	0,16	0,28	0,14	0,40	0,24	0,52	0,176 (0,053)	0,40 (0,12)
0,42	0,24	0,52	0,20	0,69	0,32	0,84	0,251 (0,063)	0,68 (0,16)
0,49	0,33	0,85	0,27	1,08	0,41	1,26	0,337 (0,074)	1,06 (0,20)
0,58	0,44	1,29	0,34	1,57	0,52	1,78	0,433 (0,086)	1,55 (0,25)
0,67	0,54	1,83	0,42	2,19	0,62	2,42	0,527 (0,098)	2,14 (0,29)
0,78	0,65	2,48	0,50	2,91	0,71	3,15	0,62 (0,11)	2,85 (0,34)
0,91	0,70	3,18	0,54	3,69	0,76	3,94	0,67 (0,11)	3,60 (0,39)
1,06	0,74	3,92	0,58	4,53	0,80	4,76	0,71 (0,11)	4,40 (0,43)
1,24	0,76	4,68	0,59	5,38	0,81	5,60	0,72 (0,11)	5,22 (0,48)
1,44	0,74	5,42	0,58	6,22	0,79	6,41	0,70 (0,11)	6,02 (0,53)
1,68	0,69	6,11	0,55	7,01	0,75	7,18	0,66 (0,10)	6,77 (0,58)
1,95	0,62	6,73	0,50	7,74	0,69	7,89	0,604 (0,096)	7,45 (0,63)
2,28	0,56	7,29	0,45	8,39	0,63	8,54	0,545 (0,090)	8,07 (0,68)
2,65	0,50	7,79	0,40	8,97	0,58	9,13	0,492 (0,085)	8,63 (0,73)
3,09	0,45	8,24	0,37	9,51	0,54	9,68	0,452 (0,083)	9,14 (0,79)
3,60	0,43	8,67	0,35	10,02	0,51	10,20	0,429 (0,082)	9,63 (0,84)
4,19	0,42	9,09	0,34	10,52	0,51	10,71	0,424 (0,082)	10,11 (0,89)
4,88	0,44	9,53	0,36	11,04	0,52	11,24	0,439 (0,082)	10,60 (0,94)
5,69	0,47	10,00	0,39	11,60	0,56	11,80	0,474 (0,085)	11,13 (0,99)
6,63	0,53	10,53	0,44	12,24	0,62	12,43	0,530 (0,090)	11,7 (1,0)
7,72	0,62	11,15	0,52	12,99	0,71	13,15	0,615 (0,098)	12,4 (1,1)
9,00	0,74	11,89	0,62	13,89	0,85	14,01	0,74 (0,11)	13,3 (1,2)
10,48	0,91	12,79	0,77	15,01	1,04	15,07	0,91 (0,13)	14,3 (1,3)
12,21	1,14	13,93	0,97	16,42	1,29	16,38	1,13 (0,16)	15,6 (1,4)
14,22	1,44	15,37	1,23	18,19	1,60	18,00	1,42 (0,18)	17,2 (1,6)
16,57	1,82	17,20	1,54	20,42	1,95	19,98	1,77 (0,21)	19,2 (1,7)
19,31	2,28	19,48	1,91	23,18	2,34	22,34	2,18 (0,23)	21,7 (1,9)
22,49	2,79	22,27	2,31	26,53	2,73	25,09	2,61 (0,26)	24,6 (2,2)
26,20	3,33	25,60	2,72	30,46	3,08	28,20	3,04 (0,31)	28,1 (2,4)
30,53	3,85	29,45	3,10	34,95	3,36	31,59	3,44 (0,38)	32,0 (2,8)
35,56	4,31	33,77	3,41	39,88	3,55	35,21	3,76 (0,48)	36,3 (3,2)
41,43	4,68	38,45	3,64	45,14	3,65	38,96	3,99 (0,60)	40,8 (3,7)
48,27	4,93	43,38	3,74	50,53	3,66	42,77	4,11 (0,71)	45,6 (4,3)
56,23	5,06	48,43	3,73	55,91	3,60	46,57	4,13 (0,81)	50,3 (4,9)
65,51	5,07	53,51	3,62	61,12	3,50	50,31	4,06 (0,88)	55,0 (5,6)
76,32	5,00	58,51	3,43	66,05	3,37	53,93	3,93 (0,93)	59,5 (6,1)
88,91	4,88	63,39	3,18	70,65	3,24	57,37	3,77 (0,96)	63,8 (6,6)
103,58	4,72	68,12	2,90	74,89	3,11	60,60	3,58 (1,00)	67,9 (7,1)
120,67	4,56	72,67	2,62	78,79	3,00	63,58	3,4 (1,0)	71,7 (7,7)
140,58	4,38	77,05	2,41	82,43	2,92	66,32	3,2 (1,0)	75,3 (8,2)
163,77	4,26	81,31	2,25	85,96	2,91	68,88	3,1 (1,0)	78,7 (8,8)
190,80	4,13	85,45	2,10	89,41	2,97	71,37	3,1 (1,0)	82,1 (9,5)
222,28	3,93	89,37	1,90	92,69	3,15	73,89	3,0 (1,0)	85 (10)
258,95	3,57	92,95	1,57	95,60	3,40	76,51	2,8 (1,1)	88 (10)
301,68	3,01	95,96	1,15	97,90	3,84	79,67	2,7 (1,4)	91 (10)
351,46	2,24	98,20	0,63	99,33	4,21	83,44	2,4 (1,8)	93,7 (8,9)
409,45	1,33	99,53	0,22	100,00	4,33	87,63	2,0 (2,1)	95,7 (7,0)
477,01	0,42	99,95	0,00	100,00	3,98	91,79	1,5 (2,2)	97,2 (4,7)
555,71	0,05	100,00	0,00	100,00	3,14	95,35	1,1 (1,8)	98,4 (2,7)
647,41	0,00	100,00	0,00	100,00	2,08	97,90	0,7 (1,2)	99,3 (1,2)
754,23	0,00	100,00	0,00	100,00	1,02	99,45	0,34 (0,59)	99,82 (0,32)
878,67	0,00	100,00	0,00	100,00	0,26	100,00	0,09 (0,15)	100 (0)

Table Ap.V.3 Data on particle size distribution of #2 chewed standard meal

Particle size (μm)	1st measurement		2nd measurement		3rd measurement		Mean (SD)	
	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)
0,06	0,00	0,00	0,00	0,00	0,00	0,00	0,00011 (0,00019)	0,00 (0,00)
0,07	0,00	0,00	0,00	0,00	0,00	0,00	0,00029 (0,00048)	0,00 (0,00)
0,08	0,00	0,00	0,00	0,00	0,00	0,00	0,0007 (0,0010)	0,00019 (0,00016)
0,09	0,00	0,00	0,00	0,00	0,00	0,00	0,0016 (0,0020)	0,0010 (0,0008)
0,11	0,00	0,00	0,00	0,00	0,01	0,01	0,0037 (0,0037)	0,0036 (0,0024)
0,13	0,01	0,01	0,00	0,00	0,02	0,02	0,0081 (0,0065)	0,0102 (0,0057)
0,15	0,02	0,03	0,01	0,01	0,03	0,04	0,016 (0,011)	0,025 (0,012)
0,17	0,03	0,06	0,01	0,03	0,05	0,08	0,031 (0,017)	0,056 (0,022)
0,20	0,06	0,12	0,03	0,07	0,08	0,15	0,054 (0,025)	0,112 (0,036)
0,23	0,10	0,21	0,05	0,15	0,12	0,26	0,089 (0,036)	0,208 (0,056)
0,27	0,15	0,36	0,08	0,27	0,18	0,43	0,136 (0,049)	0,357 (0,081)
0,31	0,22	0,58	0,12	0,46	0,24	0,68	0,195 (0,063)	0,58 (0,11)
0,36	0,29	0,87	0,17	0,72	0,32	1,02	0,261 (0,077)	0,87 (0,15)
0,42	0,37	1,24	0,23	1,06	0,40	1,44	0,331 (0,092)	1,25 (0,19)
0,49	0,46	1,70	0,29	1,49	0,49	1,96	0,41 (0,11)	1,72 (0,24)
0,58	0,56	2,25	0,36	2,03	0,59	2,60	0,50 (0,13)	2,29 (0,29)
0,67	0,65	2,91	0,42	2,66	0,68	3,34	0,58 (0,14)	2,97 (0,34)
0,78	0,74	3,65	0,49	3,40	0,77	4,18	0,67 (0,16)	3,74 (0,40)
0,91	0,80	4,45	0,53	4,19	0,83	5,09	0,72 (0,16)	4,58 (0,46)
1,06	0,84	5,29	0,57	5,05	0,87	6,04	0,76 (0,17)	5,46 (0,52)
1,24	0,86	6,15	0,59	5,93	0,89	7,02	0,78 (0,17)	6,37 (0,58)
1,44	0,86	7,00	0,59	6,81	0,89	7,99	0,78 (0,16)	7,27 (0,63)
1,68	0,83	7,83	0,57	7,67	0,86	8,93	0,75 (0,16)	8,14 (0,68)
1,95	0,79	8,62	0,54	8,49	0,81	9,81	0,71 (0,15)	8,97 (0,73)
2,28	0,74	9,36	0,51	9,25	0,76	10,64	0,67 (0,14)	9,75 (0,77)
2,65	0,71	10,06	0,48	9,97	0,71	11,41	0,63 (0,13)	10,48 (0,81)
3,09	0,68	10,75	0,46	10,66	0,68	12,15	0,61 (0,13)	11,18 (0,84)
3,60	0,67	11,42	0,44	11,33	0,66	12,86	0,59 (0,13)	11,87 (0,86)
4,19	0,68	12,10	0,44	11,99	0,67	13,57	0,60 (0,13)	12,56 (0,88)
4,88	0,71	12,82	0,46	12,68	0,69	14,31	0,62 (0,14)	13,27 (0,90)
5,69	0,76	13,58	0,49	13,42	0,74	15,10	0,66 (0,15)	14,03 (0,93)
6,63	0,83	14,41	0,53	14,21	0,81	15,97	0,73 (0,17)	14,86 (0,97)
7,72	0,92	15,33	0,59	15,10	0,92	16,96	0,81 (0,19)	15,8 (1,0)
9,00	1,06	16,39	0,68	16,12	1,07	18,10	0,94 (0,22)	16,9 (1,1)
10,48	1,24	17,63	0,80	17,33	1,26	19,46	1,10 (0,26)	18,1 (1,2)
12,21	1,50	19,13	0,97	18,78	1,52	21,10	1,33 (0,31)	19,7 (1,3)
14,22	1,83	20,96	1,19	20,56	1,86	23,11	1,62 (0,38)	21,5 (1,4)
16,57	2,25	23,21	1,46	22,76	2,27	25,56	1,99 (0,46)	23,8 (1,5)
19,31	2,73	25,94	1,79	25,46	2,75	28,52	2,42 (0,55)	26,6 (1,6)
22,49	3,25	29,19	2,17	28,72	3,27	32,05	2,90 (0,63)	30,0 (1,8)
26,20	3,76	32,95	2,56	32,58	3,80	36,14	3,37 (0,70)	33,9 (2,0)
30,53	4,20	37,15	2,93	37,00	4,27	40,73	3,80 (0,75)	38,3 (2,1)
35,56	4,51	41,65	3,24	41,88	4,64	45,71	4,13 (0,77)	43,1 (2,3)
41,43	4,64	46,30	3,45	47,06	4,84	50,90	4,31 (0,75)	48,1 (2,5)
48,27	4,59	50,88	3,52	52,35	4,85	56,11	4,32 (0,70)	53,1 (2,7)
56,23	4,36	55,25	3,46	57,54	4,66	61,12	4,16 (0,63)	58,0 (3,0)
65,51	4,03	59,28	3,28	62,48	4,33	65,76	3,88 (0,54)	62,5 (3,2)
76,32	3,68	62,96	3,03	67,04	3,92	69,93	3,54 (0,46)	66,6 (3,5)
88,91	3,38	66,34	2,74	71,19	3,51	73,60	3,21 (0,41)	70,4 (3,7)
103,58	3,19	69,53	2,47	74,96	3,16	76,78	2,94 (0,41)	73,8 (3,8)
120,67	3,11	72,64	2,30	78,45	2,91	79,49	2,77 (0,42)	76,9 (3,7)
140,58	3,24	75,89	2,22	81,87	2,90	82,22	2,79 (0,52)	80,0 (3,6)
163,77	3,74	79,63	2,31	85,44	3,19	85,24	3,08 (0,72)	83,4 (3,3)
190,80	4,25	83,89	2,40	89,12	3,72	88,66	3,46 (0,95)	87,2 (2,9)
222,28	4,54	88,43	2,37	92,69	4,16	92,34	3,7 (1,2)	91,2 (2,4)
258,95	4,39	92,81	2,12	95,82	4,20	95,84	3,6 (1,3)	94,8 (1,7)
301,68	3,66	96,48	1,64	98,13	3,62	98,54	3,0 (1,2)	97,7 (1,1)
351,46	2,43	98,91	0,99	99,47	2,41	99,92	1,94 (0,83)	99,43 (0,51)
409,45	1,08	99,99	0,49	99,96	1,02	100,00	0,86 (0,32)	99,983 (0,019)
477,01	0,01	100,00	0,04	100,00	0,13	100,00	0,060 (0,062)	100 (0)
555,71	0,00	100,00	0,00	100,00	0,00	100,00	0,00 (0,00)	100 (0)
647,41	0,00	100,00	0,00	100,00	0,00	100,00	0,00 (0,00)	100 (0)
754,23	0,00	100,00	0,00	100,00	0,00	100,00	0,00 (0,00)	100 (0)
878,67	0,00	100,00	0,00	100,00	0,00	100,00	0,00 (0,00)	100 (0)

Table Ap.V.4 Data on particle size distribution of #3 chewed standard meal

Particle size (μm)	1st measurement		2nd measurement		3rd measurement		Mean (SD)	
	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)
0,06	0,00	0,00	0,00	0,00	0,00	0,00	0,00229 (0,00075)	0,0020 (0,0010)
0,07	0,00	0,01	0,01	0,01	0,00	0,00	0,00462 (0,00064)	0,0066 (0,0031)
0,08	0,01	0,01	0,01	0,02	0,01	0,01	0,00809 (0,00076)	0,0150 (0,0066)
0,09	0,01	0,03	0,01	0,04	0,02	0,02	0,0135 (0,0014)	0,030 (0,012)
0,11	0,02	0,05	0,02	0,07	0,03	0,04	0,0221 (0,0028)	0,054 (0,018)
0,13	0,04	0,08	0,03	0,12	0,04	0,07	0,0352 (0,0053)	0,092 (0,026)
0,15	0,06	0,14	0,04	0,19	0,06	0,13	0,0545 (0,0093)	0,153 (0,035)
0,17	0,09	0,22	0,07	0,29	0,10	0,21	0,082 (0,015)	0,244 (0,043)
0,20	0,12	0,35	0,09	0,44	0,14	0,35	0,119 (0,024)	0,377 (0,050)
0,23	0,18	0,52	0,13	0,63	0,20	0,54	0,167 (0,035)	0,565 (0,055)
0,27	0,24	0,76	0,17	0,88	0,27	0,82	0,226 (0,050)	0,821 (0,060)
0,31	0,31	1,07	0,22	1,21	0,35	1,19	0,293 (0,066)	1,155 (0,072)
0,36	0,39	1,46	0,27	1,60	0,43	1,65	0,364 (0,083)	1,572 (0,099)
0,42	0,47	1,93	0,33	2,08	0,52	2,22	0,44 (0,10)	2,08 (0,14)
0,49	0,56	2,49	0,38	2,64	0,61	2,89	0,52 (0,12)	2,67 (0,20)
0,58	0,64	3,13	0,44	3,28	0,71	3,67	0,60 (0,14)	3,36 (0,28)
0,67	0,72	3,85	0,50	4,00	0,79	4,56	0,67 (0,16)	4,14 (0,37)
0,78	0,79	4,64	0,54	4,79	0,87	5,53	0,73 (0,17)	4,99 (0,47)
0,91	0,80	5,45	0,55	5,59	0,89	6,52	0,75 (0,17)	5,85 (0,58)
1,06	0,80	6,25	0,56	6,40	0,89	7,51	0,75 (0,17)	6,72 (0,69)
1,24	0,79	7,04	0,55	7,19	0,87	8,48	0,73 (0,17)	7,57 (0,79)
1,44	0,75	7,78	0,52	7,95	0,83	9,41	0,70 (0,16)	8,38 (0,90)
1,68	0,69	8,47	0,48	8,65	0,77	10,26	0,65 (0,15)	9,13 (0,99)
1,95	0,63	9,11	0,44	9,30	0,70	11,04	0,59 (0,13)	9,8 (1,1)
2,28	0,58	9,69	0,41	9,89	0,64	11,75	0,55 (0,12)	10,4 (1,1)
2,65	0,55	10,23	0,38	10,45	0,60	12,41	0,51 (0,11)	11,0 (1,2)
3,09	0,52	10,76	0,37	10,99	0,57	13,04	0,49 (0,11)	11,6 (1,3)
3,60	0,52	11,28	0,36	11,52	0,56	13,65	0,48 (0,10)	12,1 (1,3)
4,19	0,52	11,80	0,37	12,05	0,56	14,26	0,49 (0,10)	12,7 (1,4)
4,88	0,54	12,34	0,38	12,61	0,58	14,90	0,50 (0,11)	13,3 (1,4)
5,69	0,57	12,91	0,40	13,19	0,62	15,57	0,53 (0,11)	13,9 (1,5)
6,63	0,61	13,53	0,44	13,83	0,68	16,30	0,58 (0,12)	14,6 (1,5)
7,72	0,69	14,21	0,49	14,54	0,76	17,13	0,65 (0,14)	15,3 (1,6)
9,00	0,81	15,02	0,57	15,38	0,90	18,09	0,76 (0,17)	16,2 (1,7)
10,48	0,98	16,00	0,70	16,39	1,09	19,27	0,92 (0,20)	17,2 (1,8)
12,21	1,22	17,22	0,86	17,64	1,34	20,71	1,14 (0,25)	18,5 (1,9)
14,22	1,52	18,75	1,07	19,19	1,67	22,50	1,42 (0,31)	20,1 (2,0)
16,57	1,87	20,62	1,30	21,07	2,04	24,68	1,74 (0,38)	22,1 (2,2)
19,31	2,24	22,86	1,55	23,31	2,42	27,29	2,07 (0,46)	24,5 (2,4)
22,49	2,57	25,43	1,77	25,87	2,78	30,30	2,37 (0,53)	27,2 (2,7)
26,20	2,82	28,25	1,94	28,66	3,06	33,62	2,60 (0,59)	30,2 (3,0)
30,53	2,94	31,19	2,01	31,56	3,21	37,13	2,72 (0,63)	33,3 (3,3)
35,56	2,92	34,10	2,00	34,43	3,23	40,69	2,71 (0,64)	36,4 (3,7)
41,43	2,77	36,87	1,90	37,17	3,12	44,14	2,60 (0,63)	39,4 (4,1)
48,27	2,55	39,42	1,75	39,70	2,94	47,40	2,41 (0,61)	42,2 (4,5)
56,23	2,33	41,75	1,61	42,02	2,77	50,44	2,23 (0,59)	44,7 (4,9)
65,51	2,09	43,84	1,52	44,21	2,67	53,31	2,09 (0,58)	47,1 (5,4)
76,32	2,12	45,96	1,54	46,44	2,71	56,14	2,12 (0,59)	49,5 (5,7)
88,91	2,38	48,34	1,69	48,89	2,94	59,10	2,34 (0,62)	52,1 (6,1)
103,58	2,88	51,23	2,00	51,78	3,35	62,35	2,75 (0,69)	55,1 (6,3)
120,67	3,62	54,84	2,43	55,30	3,92	66,06	3,32 (0,79)	58,7 (6,4)
140,58	4,53	59,37	2,96	59,56	4,58	70,33	4,02 (0,92)	63,1 (6,3)
163,77	5,55	64,92	3,53	64,65	5,29	75,18	4,8 (1,1)	68,2 (6,0)
190,80	6,64	71,56	4,13	70,59	5,94	80,61	5,6 (1,3)	74,3 (5,5)
222,28	7,23	78,79	4,44	77,09	6,19	86,28	5,9 (1,4)	80,7 (4,9)
258,95	7,13	85,92	4,37	83,59	5,87	91,63	5,8 (1,4)	87,0 (4,1)
301,68	6,24	92,16	3,86	89,53	4,92	96,00	5,0 (1,2)	92,6 (3,3)
351,46	4,63	96,79	2,95	94,34	3,38	98,79	3,66 (0,87)	96,6 (2,2)
409,45	2,59	99,38	1,76	97,60	1,71	100,00	2,02 (0,49)	99,0 (1,2)
477,01	0,62	100,00	0,58	99,23	0,30	100,00	0,50 (0,17)	99,74 (0,45)
555,71	0,00	100,00	0,00	99,84	0,00	100,00	0,00053 (0,00091)	99,95 (0,10)
647,41	0,00	100,00	0,00	100,00	0,00	100,00	0,00053 (0,00091)	100 (0)
754,23	0,00	100,00	0,00	100,00	0,00	100,00	0,00053 (0,00091)	100 (0)
878,67	0,00	100,00	0,00	100,00	0,00	100,00	0,00053 (0,00091)	100 (0)

Table Ap.V.5 Data on particle size distribution of #1 homogenized standard meal

Particle size (µm)	1st measurement		2nd measurement		3rd measurement		Mean (SD)	
	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)
0,06	0,00	0,00	0,01	0,01	0,01	0,01	0,0065 (0,0044)	0,0060 (0,0044)
0,07	0,00	0,01	0,02	0,03	0,01	0,02	0,0123 (0,0072)	0,019 (0,013)
0,08	0,01	0,01	0,03	0,07	0,02	0,04	0,019 (0,010)	0,039 (0,027)
0,09	0,01	0,02	0,04	0,12	0,03	0,06	0,027 (0,014)	0,068 (0,046)
0,11	0,02	0,04	0,05	0,18	0,05	0,10	0,036 (0,017)	0,108 (0,070)
0,13	0,02	0,06	0,06	0,26	0,06	0,16	0,046 (0,021)	0,159 (0,099)
0,15	0,03	0,09	0,07	0,36	0,08	0,23	0,058 (0,024)	0,22 (0,13)
0,17	0,04	0,13	0,08	0,47	0,09	0,31	0,070 (0,028)	0,30 (0,17)
0,20	0,05	0,18	0,09	0,60	0,11	0,42	0,084 (0,031)	0,40 (0,21)
0,23	0,06	0,25	0,10	0,74	0,13	0,55	0,098 (0,033)	0,51 (0,25)
0,27	0,08	0,33	0,11	0,90	0,15	0,71	0,112 (0,036)	0,64 (0,29)
0,31	0,10	0,42	0,11	1,06	0,17	0,88	0,125 (0,037)	0,79 (0,33)
0,36	0,11	0,54	0,12	1,24	0,18	1,08	0,138 (0,039)	0,95 (0,37)
0,42	0,13	0,67	0,12	1,42	0,20	1,29	0,152 (0,041)	1,13 (0,40)
0,49	0,16	0,83	0,13	1,61	0,22	1,54	0,171 (0,047)	1,33 (0,43)
0,58	0,20	1,03	0,14	1,82	0,25	1,82	0,197 (0,056)	1,56 (0,46)
0,67	0,24	1,27	0,16	2,05	0,30	2,15	0,232 (0,070)	1,82 (0,48)
0,78	0,30	1,58	0,18	2,32	0,35	2,55	0,280 (0,088)	2,15 (0,51)
0,91	0,38	1,96	0,23	2,66	0,44	3,04	0,35 (0,11)	2,56 (0,55)
1,06	0,47	2,43	0,28	3,07	0,54	3,65	0,43 (0,13)	3,05 (0,61)
1,24	0,55	2,98	0,33	3,56	0,63	4,35	0,51 (0,16)	3,63 (0,69)
1,44	0,64	3,62	0,38	4,14	0,73	5,17	0,59 (0,18)	4,31 (0,79)
1,68	0,72	4,34	0,44	4,80	0,83	6,10	0,66 (0,20)	5,08 (0,91)
1,95	0,80	5,14	0,50	5,55	0,91	7,12	0,74 (0,21)	5,9 (1,0)
2,28	0,88	6,02	0,55	6,38	0,99	8,23	0,81 (0,23)	6,9 (1,2)
2,65	0,96	6,98	0,60	7,28	1,06	9,41	0,87 (0,24)	7,9 (1,3)
3,09	1,04	8,02	0,64	8,23	1,11	10,64	0,93 (0,26)	9,0 (1,5)
3,60	1,13	9,15	0,66	9,23	1,15	11,92	0,98 (0,28)	10,1 (1,6)
4,19	1,23	10,38	0,67	10,25	1,17	13,22	1,03 (0,31)	11,3 (1,7)
4,88	1,33	11,72	0,66	11,25	1,17	14,52	1,06 (0,35)	12,5 (1,8)
5,69	1,43	13,15	0,63	12,21	1,15	15,77	1,07 (0,40)	13,7 (1,8)
6,63	1,51	14,66	0,58	13,08	1,09	16,95	1,06 (0,47)	14,9 (1,9)
7,72	1,57	16,23	0,50	13,83	1,00	18,03	1,02 (0,53)	16,0 (2,1)
9,00	1,61	17,84	0,42	14,46	0,88	18,97	0,97 (0,60)	17,1 (2,3)
10,48	1,63	19,48	0,34	14,97	0,77	19,78	0,92 (0,66)	18,1 (2,7)
12,21	1,66	21,14	0,29	15,39	0,69	20,50	0,88 (0,71)	19,0 (3,2)
14,22	1,72	22,86	0,27	15,78	0,66	21,18	0,88 (0,75)	19,9 (3,7)
16,57	1,82	24,68	0,30	16,23	0,71	21,92	0,95 (0,79)	20,9 (4,3)
19,31	1,98	26,67	0,39	16,80	0,85	22,81	1,07 (0,82)	22,1 (5,0)
22,49	2,19	28,85	0,52	17,56	1,08	23,95	1,26 (0,85)	23,5 (5,7)
26,20	2,42	31,27	0,66	18,55	1,35	25,38	1,48 (0,89)	25,1 (6,4)
30,53	2,64	33,91	0,80	19,75	1,63	27,11	1,69 (0,92)	26,9 (7,1)
35,56	2,81	36,72	0,91	21,12	1,86	29,11	1,86 (0,95)	29,0 (7,8)
41,43	2,88	39,60	0,97	22,57	2,01	31,29	1,96 (0,96)	31,2 (8,5)
48,27	2,85	42,46	1,00	24,06	2,08	33,56	1,98 (0,93)	33,4 (9,2)
56,23	2,74	45,20	1,03	25,60	2,10	35,86	1,96 (0,87)	35,6 (9,8)
65,51	2,60	47,80	1,12	27,27	2,16	38,24	1,96 (0,76)	38 (10)
76,32	2,51	50,31	1,33	29,26	2,35	40,81	2,06 (0,64)	40 (11)
88,91	2,54	52,85	1,73	31,86	2,76	43,78	2,34 (0,54)	43 (11)
103,58	2,75	55,60	2,30	35,33	3,42	47,38	2,82 (0,56)	46 (10)
120,67	3,14	58,74	3,03	39,92	4,32	51,82	3,49 (0,71)	50,2 (9,5)
140,58	3,70	62,44	3,83	45,77	5,37	57,23	4,30 (0,93)	55,1 (8,5)
163,77	4,38	66,82	4,66	52,90	6,51	63,65	5,2 (1,2)	61,1 (7,3)
190,80	5,13	71,95	5,47	61,32	7,66	71,08	6,1 (1,4)	68,1 (5,9)
222,28	5,71	77,66	6,02	70,49	8,26	78,97	6,7 (1,4)	75,7 (4,6)
258,95	5,87	83,53	5,96	79,51	8,15	86,60	6,7 (1,3)	83,2 (3,6)
301,68	5,49	89,02	5,39	87,57	7,16	93,09	6,01 (0,99)	89,9 (2,9)
351,46	4,58	93,60	4,32	93,90	5,29	97,55	4,73 (0,50)	95,0 (2,2)
409,45	3,37	96,97	2,87	97,94	2,99	100,00	3,08 (0,26)	98,3 (1,5)
477,01	1,81	98,78	1,42	99,68	0,55	100,00	1,26 (0,64)	99,49 (0,63)
555,71	0,88	99,66	0,32	100,00	0,00	100,00	0,40 (0,44)	99,89 (0,20)
647,41	0,34	100,00	0,00	100,00	0,00	100,00	0,11 (0,19)	100 (0)
754,23	0,00	100,00	0,00	100,00	0,00	100,00	0,0012 (0,0021)	100 (0)
878,67	0,00	100,00	0,00	100,00	0,00	100,00	0,0012 (0,0021)	100 (0)

Table Ap.V.6 Data on particle size distribution of #2 homogenized standard meal

Particle size (µm)	1st measurement		2nd measurement		3rd measurement		Mean (SD)	
	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)
0,06	0,00	0,00	0,01	0,01	0,01	0,01	0,0051 (0,0042)	0,0051 (0,0042)
0,07	0,00	0,00	0,02	0,03	0,01	0,02	0,0101 (0,0076)	0,016 (0,013)
0,08	0,00	0,01	0,03	0,06	0,02	0,04	0,016 (0,011)	0,033 (0,026)
0,09	0,01	0,01	0,03	0,10	0,03	0,06	0,023 (0,015)	0,059 (0,044)
0,11	0,01	0,02	0,04	0,16	0,04	0,10	0,031 (0,019)	0,094 (0,068)
0,13	0,02	0,04	0,06	0,23	0,05	0,16	0,042 (0,023)	0,142 (0,097)
0,15	0,02	0,06	0,07	0,32	0,07	0,23	0,054 (0,026)	0,20 (0,13)
0,17	0,03	0,10	0,08	0,42	0,09	0,32	0,067 (0,029)	0,28 (0,17)
0,20	0,05	0,14	0,09	0,55	0,11	0,43	0,082 (0,032)	0,37 (0,21)
0,23	0,06	0,21	0,10	0,69	0,13	0,56	0,098 (0,035)	0,49 (0,25)
0,27	0,08	0,28	0,11	0,85	0,15	0,72	0,114 (0,038)	0,62 (0,30)
0,31	0,09	0,37	0,12	1,02	0,17	0,89	0,127 (0,043)	0,76 (0,35)
0,36	0,09	0,46	0,13	1,21	0,19	1,09	0,138 (0,050)	0,92 (0,40)
0,42	0,09	0,56	0,14	1,42	0,21	1,30	0,147 (0,059)	1,09 (0,47)
0,49	0,09	0,65	0,15	1,64	0,23	1,54	0,160 (0,070)	1,28 (0,54)
0,58	0,16	0,81	0,17	1,89	0,27	1,81	0,199 (0,060)	1,50 (0,60)
0,67	0,17	0,98	0,20	2,18	0,31	2,13	0,226 (0,077)	1,76 (0,68)
0,78	0,19	1,17	0,23	2,52	0,38	2,52	0,266 (0,097)	2,07 (0,78)
0,91	0,24	1,41	0,29	2,96	0,47	3,00	0,34 (0,12)	2,45 (0,91)
1,06	0,29	1,70	0,35	3,49	0,58	3,59	0,41 (0,15)	2,9 (1,1)
1,24	0,35	2,05	0,42	4,11	0,69	4,29	0,49 (0,18)	3,5 (1,2)
1,44	0,42	2,47	0,49	4,84	0,80	5,11	0,57 (0,20)	4,1 (1,5)
1,68	0,49	2,96	0,55	5,66	0,91	6,04	0,65 (0,23)	4,9 (1,7)
1,95	0,55	3,51	0,62	6,58	1,01	7,07	0,73 (0,25)	5,7 (1,9)
2,28	0,61	4,11	0,67	7,58	1,10	8,19	0,79 (0,27)	6,6 (2,2)
2,65	0,65	4,76	0,72	8,65	1,16	9,37	0,84 (0,28)	7,6 (2,5)
3,09	0,68	5,44	0,75	9,77	1,20	10,59	0,88 (0,28)	8,6 (2,8)
3,60	0,69	6,12	0,78	10,92	1,21	11,82	0,89 (0,28)	9,6 (3,1)
4,19	0,68	6,80	0,78	12,09	1,19	13,03	0,89 (0,27)	10,6 (3,4)
4,88	0,65	7,45	0,77	13,24	1,14	14,18	0,85 (0,25)	11,6 (3,6)
5,69	0,60	8,06	0,74	14,35	1,04	15,23	0,79 (0,22)	12,5 (3,9)
6,63	0,53	8,59	0,68	15,35	0,89	16,12	0,70 (0,18)	13,4 (4,1)
7,72	0,44	9,02	0,59	16,22	0,70	16,83	0,58 (0,13)	14,0 (4,3)
9,00	0,33	9,35	0,48	16,93	0,50	17,33	0,436 (0,093)	14,5 (4,5)
10,48	0,23	9,58	0,37	17,47	0,32	17,64	0,302 (0,071)	14,9 (4,6)
12,21	0,14	9,72	0,27	17,87	0,18	17,82	0,196 (0,067)	15,1 (4,7)
14,22	0,10	9,82	0,22	18,19	0,10	17,92	0,141 (0,071)	15,3 (4,8)
16,57	0,10	9,92	0,24	18,53	0,12	18,04	0,152 (0,073)	15,5 (4,8)
19,31	0,16	10,08	0,32	19,01	0,23	18,27	0,239 (0,080)	15,8 (5,0)
22,49	0,28	10,37	0,48	19,72	0,44	18,71	0,40 (0,11)	16,3 (5,1)
26,20	0,45	10,81	0,69	20,74	0,74	19,45	0,63 (0,16)	17,0 (5,4)
30,53	0,63	11,44	0,92	22,10	1,09	20,54	0,88 (0,24)	18,0 (5,8)
35,56	0,79	12,22	1,11	23,74	1,42	21,97	1,10 (0,32)	19,3 (6,2)
41,43	0,89	13,11	1,23	25,57	1,65	23,64	1,26 (0,38)	20,8 (6,7)
48,27	0,91	14,03	1,28	27,46	1,77	25,44	1,32 (0,43)	22,3 (7,2)
56,23	0,89	14,91	1,27	29,32	1,78	27,28	1,31 (0,45)	23,8 (7,8)
65,51	0,88	15,79	1,13	30,90	1,79	29,16	1,27 (0,48)	25,3 (8,3)
76,32	0,96	16,75	1,18	32,55	1,93	31,20	1,36 (0,51)	26,8 (8,8)
88,91	1,23	17,98	1,38	34,51	2,31	33,64	1,64 (0,58)	28,7 (9,3)
103,58	1,74	19,72	1,77	37,07	2,99	36,76	2,17 (0,71)	31,2 (9,9)
120,67	2,53	22,26	2,36	40,53	3,96	40,84	2,95 (0,88)	35 (11)
140,58	3,56	25,81	3,11	45,16	5,12	46,05	3,9 (1,1)	39 (11)
163,77	4,73	30,54	3,95	51,11	6,34	52,42	5,0 (1,2)	45 (12)
190,80	5,96	36,50	4,84	58,48	7,59	59,96	6,1 (1,4)	52 (13)
222,28	7,09	43,60	5,75	67,31	8,85	68,69	7,2 (1,6)	60 (14)
258,95	8,07	51,67	5,92	76,43	8,98	77,49	7,7 (1,6)	69 (15)
301,68	8,93	60,59	5,46	84,82	8,21	85,52	7,5 (1,8)	77 (14)
351,46	9,31	69,90	4,42	91,58	6,63	92,01	6,8 (2,4)	84 (13)
409,45	8,67	78,57	3,06	96,23	4,76	96,55	5,5 (2,9)	90 (10)
477,01	7,33	85,90	1,78	98,90	2,93	99,21	4,0 (2,9)	94,7 (7,6)
555,71	5,91	91,81	0,67	99,84	0,69	100,00	2,4 (3,0)	97,2 (4,7)
647,41	4,39	96,20	0,16	100,00	0,00	100,00	1,5 (2,5)	98,7 (2,2)
754,23	2,73	98,94	0,00	100,00	0,00	100,00	0,9 (1,6)	99,65 (0,61)
878,67	1,06	100,00	0,00	100,00	0,00	100,00	0,36 (0,61)	100 (0)

Table Ap.V.7 Data on particle size distribution of #3 homogenized standard meal

Particle size (µm)	1st measurement		2nd measurement		3rd measurement		Mean (SD)	
	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)	Result (%)	Cumulative result (%)
0,06	0,00	0,00	0,00	0,00	0,00	0,00	0,0012 (0,0010)	0,0008 (0,0010)
0,07	0,00	0,01	0,00	0,00	0,00	0,00	0,0026 (0,0023)	0,0026 (0,0032)
0,08	0,01	0,01	0,00	0,00	0,01	0,00	0,0043 (0,0038)	0,0058 (0,0067)
0,09	0,01	0,02	0,00	0,00	0,01	0,01	0,0067 (0,0058)	0,011 (0,012)
0,11	0,02	0,04	0,00	0,00	0,01	0,02	0,0098 (0,0085)	0,019 (0,020)
0,13	0,02	0,06	0,00	0,00	0,02	0,03	0,014 (0,012)	0,030 (0,031)
0,15	0,03	0,09	0,00	0,00	0,03	0,05	0,019 (0,017)	0,047 (0,045)
0,17	0,04	0,13	0,00	0,00	0,04	0,08	0,026 (0,023)	0,070 (0,065)
0,20	0,05	0,18	0,00	0,00	0,05	0,13	0,035 (0,029)	0,102 (0,091)
0,23	0,06	0,24	0,01	0,02	0,07	0,19	0,049 (0,033)	0,15 (0,12)
0,27	0,08	0,32	0,03	0,06	0,09	0,27	0,067 (0,033)	0,22 (0,14)
0,31	0,10	0,42	0,05	0,14	0,12	0,39	0,090 (0,033)	0,32 (0,15)
0,36	0,12	0,54	0,09	0,27	0,15	0,53	0,117 (0,031)	0,45 (0,16)
0,42	0,14	0,68	0,12	0,45	0,19	0,72	0,149 (0,032)	0,62 (0,15)
0,49	0,16	0,84	0,17	0,71	0,23	0,97	0,189 (0,037)	0,84 (0,13)
0,58	0,20	1,04	0,23	1,06	0,29	1,27	0,239 (0,046)	1,12 (0,13)
0,67	0,24	1,28	0,30	1,51	0,36	1,66	0,298 (0,060)	1,48 (0,19)
0,78	0,29	1,57	0,37	2,07	0,44	2,13	0,370 (0,077)	1,93 (0,31)
0,91	0,36	1,93	0,46	2,78	0,55	2,72	0,456 (0,097)	2,48 (0,48)
1,06	0,42	2,35	0,55	3,62	0,65	3,42	0,54 (0,12)	3,13 (0,68)
1,24	0,49	2,84	0,64	4,58	0,76	4,23	0,63 (0,13)	3,88 (0,92)
1,44	0,56	3,39	0,72	5,67	0,85	5,14	0,71 (0,15)	4,7 (1,2)
1,68	0,62	4,01	0,79	6,87	0,94	6,14	0,79 (0,16)	5,7 (1,5)
1,95	0,69	4,70	0,86	8,17	1,02	7,23	0,86 (0,17)	6,7 (1,8)
2,28	0,76	5,45	0,94	9,59	1,10	8,40	0,93 (0,17)	7,8 (2,1)
2,65	0,84	6,29	1,02	11,13	1,20	9,67	1,02 (0,18)	9,0 (2,5)
3,09	0,93	7,23	1,12	12,83	1,30	11,04	1,12 (0,18)	10,4 (2,9)
3,60	1,04	8,27	1,24	14,71	1,43	12,56	1,24 (0,19)	11,8 (3,3)
4,19	1,17	9,44	1,38	16,79	1,57	14,22	1,37 (0,20)	13,5 (3,7)
4,88	1,29	10,73	1,52	19,09	1,72	16,04	1,51 (0,21)	15,3 (4,2)
5,69	1,41	12,14	1,65	21,60	1,85	18,00	1,64 (0,22)	17,2 (4,8)
6,63	1,51	13,65	1,76	24,26	1,94	20,06	1,74 (0,22)	19,3 (5,3)
7,72	1,57	15,22	1,82	27,01	1,99	22,17	1,80 (0,21)	21,5 (5,9)
9,00	1,61	16,83	1,84	29,80	1,99	24,28	1,82 (0,20)	23,6 (6,5)
10,48	1,62	18,44	1,84	32,57	1,97	26,36	1,81 (0,18)	25,8 (7,1)
12,21	1,63	20,07	1,83	35,32	1,96	28,41	1,80 (0,17)	27,9 (7,6)
14,22	1,66	21,73	1,86	38,11	2,01	30,52	1,84 (0,18)	30,1 (8,2)
16,57	1,74	23,47	1,96	41,05	2,17	32,79	1,96 (0,21)	32,4 (8,8)
19,31	1,89	25,35	2,15	44,28	2,46	35,36	2,17 (0,29)	35,0 (9,5)
22,49	2,09	27,44	2,44	47,94	2,88	38,38	2,47 (0,39)	38 (10)
26,20	2,33	29,77	2,81	52,15	3,37	41,92	2,83 (0,52)	41 (11)
30,53	2,56	32,33	3,20	56,94	3,85	45,99	3,20 (0,64)	45 (12)
35,56	2,74	35,07	3,58	62,29	4,21	50,46	3,51 (0,74)	49 (14)
41,43	2,81	37,88	3,93	68,13	4,38	55,13	3,71 (0,81)	54 (15)
48,27	2,78	40,67	4,08	74,24	4,30	59,74	3,72 (0,82)	58 (17)
56,23	2,67	43,34	3,86	80,05	4,01	64,05	3,52 (0,73)	62 (18)
65,51	2,54	45,88	3,45	85,24	3,58	67,89	3,19 (0,57)	66 (20)
76,32	2,46	48,34	2,94	89,66	3,12	71,19	2,84 (0,34)	70 (21)
88,91	2,53	50,87	2,42	93,30	2,73	73,95	2,56 (0,16)	73 (21)
103,58	2,80	53,68	1,91	96,16	2,45	76,18	2,39 (0,45)	75 (21)
120,67	3,29	56,97	1,39	98,25	2,44	78,39	2,38 (0,95)	78 (21)
140,58	3,97	60,95	0,88	99,56	2,77	80,87	2,5 (1,6)	80 (19)
163,77	4,79	65,73	0,34	99,90	3,30	83,78	2,8 (2,3)	83 (17)
190,80	5,70	71,43	0,10	100,00	3,89	87,13	3,2 (2,9)	86 (14)
222,28	6,39	77,82	0,00	100,00	4,23	90,70	3,5 (3,2)	90 (11)
258,95	6,57	84,39	0,00	100,00	4,08	94,09	3,5 (3,3)	92,8 (7,9)
301,68	6,08	90,47	0,00	100,00	3,30	96,77	3,1 (3,0)	95,7 (4,8)
351,46	4,90	95,37	0,00	100,00	2,28	98,74	2,4 (2,5)	98,0 (2,4)
409,45	3,19	98,56	0,00	100,00	1,25	100,00	1,5 (1,6)	99,52 (0,83)
477,01	1,41	99,97	0,00	100,00	0,00	100,00	0,47 (0,81)	99,989 (0,019)
555,71	0,03	100,00	0,00	100,00	0,00	100,00	0,011 (0,019)	100 (0)
647,41	0,00	100,00	0,00	100,00	0,00	100,00	0 (0)	100 (0)
754,23	0,00	100,00	0,00	100,00	0,00	100,00	0 (0)	100 (0)
878,67	0,00	100,00	0,00	100,00	0,00	100,00	0 (0)	100 (0)

APPENDIX VI Drugs and phenol red concentrations data

Table Ap.VI.1. Paracetamol data (μg/mL) after administration of aqueous paracetamol solution (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	1487.03	866.13	49.95	131.01	1442.46	546.63	1706.56	519.94	843 (637)
		75	586.86	175.77	40.50	58.78	310.10	406.58	632.30	249.72	307 (222)
		135	50.97	64.95	72.50	25.51	114.14	286.30	311.60	119.36	130 (108)
		195	20.16	36.79	65.95	15.31	76.30	147.44	131.01	43.46	67 (49)
	Aqueous phase	15	1355.54	765.57	69.46	123.15	793.49	497.13	1557.43	917.18	760 (530)
		75	378.97	183.00	na	64.70	278.02	390.25	610.14	200.10	301 (178)
		135	41.10	59.26	59.10	25.17	105.52	na	316.38	105.15	102 (99)
		195	na	33.43	na	15.18	58.74	na	123.96	44.14	55 (42)
Upper Small Intestine	Total aspirate	30	496.21	99.32	401.23	21.55	295.54	4.93	29.32	300.80	206 (191)
		60	72.90	30.82	401.57	17.00	210.92	229.61	35.92	132.64	141 (133)
		90	32.14	13.83	134.89	9.18	200.31	215.76	15.85	89.17	89 (85)
		120	25.81	18.26	49.86	15.32	72.30	95.56	149.73	67.23	62 (46)
		150	11.12	25.85	na	8.66	67.72	100.59	206.08	44.19	66 (70)
		180	5.70	12.52	27.49	7.86	34.62	60.21	135.23	33.23	40 (43)
		210	5.53	5.66	8.95	7.65	25.54	17.45	80.88	31.06	23 (25)
		240	3.44	3.84	2.94	4.54	15.58	26.50	35.09	18.72	14 (12)
	Micellar phase	30	411.59	na	554.21	22.20	274.85	7.31	na	na	254 (240)
		60	66.89	na	402.74	15.88	189.43	221.69	na	100.68	166 (139)
		90	33.50	na	141.69	8.39	na	192.01	na	75.98	90 (76)
		120	24.80	13.12	na	12.84	na	90.93	168.46	65.90	63 (61)
		150	10.05	na	na	7.51	na	90.02	na	42.85	38 (38)
		180	5.68	17.19	27.26	7.87	35.21	60.67	na	30.56	26 (19)
		210	5.51	na	na	7.27	na	17.56	na	26.90	14 (10)
		240	3.27	na	2.38	4.37	14.26	25.11	na	18.01	11.2 (9.3)

Table Ap.VI.2. Paracetamol data (µg/mL) after administration of aqueous paracetamol suspension (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	1238.65	636.71	432.67	1508.22	824.27	840.37	1195.21	296.40	872 (419)
		75	290.02	182.67	73.26	165.13	48.13	na	101.09	116.85	140 (82)
		135	76.62	47.55	24.74	91.01	62.53	na	31.60	128.76	66 (36)
		195	30.07	27.33	13.86	44.26	na	na	17.50	51.46	31 (15)
	Aqueous phase	15	1364.64	643.02	420.23	1395.52	724.00	805.91	1052.91	288.25	837 (408)
		75	247.34	159.33	65.81	245.93	78.52	na	127.16	151.08	154 (72)
		135	77.16	44.44	25.06	81.29	na	na	26.24	na	51 (27)
		195	28.72	26.35	na	27.83	na	na	na	45.04	32.0 (8.8)
Upper Small Intestine	Total aspirate	30	306.00	159.13	10.01	818.18	93.59	131.24	105.91	144.53	221 (255)
		60	140.38	60.87	30.46	304.72	59.38	232.32	46.01	123.27	125 (98)
		90	78.78	27.69	14.72	64.20	12.33	137.84	16.34	na	50 (47)
		120	30.32	26.90	13.46	34.83	5.50	188.36	9.10	na	44 (65)
		150	33.49	21.12	6.40	36.36	2.87	132.06	5.87	na	34 (45)
		180	22.03	18.07	5.05	17.42	2.95	39.12	4.45	na	16 (13)
		210	12.52	5.88	1.28	6.74	2.08	28.61	2.25	na	8.5 (9.7)
		240	3.73	2.25	1.05	2.33	1.55	23.81	1.45	na	5.2 (8.3)
	Micellar phase	30	308.79	na	na	636.13	121.36	118.03	na	na	296 (244)
		60	141.83	58.11	na	249.88	52.42	240.19	na	na	148 (95)
		90	84.71	25.04	na	56.80	12.42	157.19	na	na	67 (58)
		120	29.71	25.13	12.12	34.74	5.34	174.50	9.13	na	42 (60)
		150	32.41	na	na	32.85	na	132.39	4.67	na	51 (56)
		180	21.69	17.98	na	18.00	2.97	na	3.82	na	12.9 (8..8)
		210	12.84	6.45	na	6.67	1.99	27.63	2.27	na	9.6 (9.6)
		240	3.73	2.19	na	2.47	1.42	na	1.30	na	2.22 (0.98)

Table Ap.VI.3. Danazol data (μg/mL) after administration of danazol sunflower oil solution (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	**15**	3.21	3.80	2.93	4.16	687.47	84.10	2.87	2561.42	419 (897)
		75	6.99	10.32	13.44	111.10	24.43	15.76	16.50	229.42	53 (79)
		135	28.06	3.93	13.27	52.50	7.33	9.55	9.75	263.83	49 (88)
		195	56.33	2.25	10.79	17.08	20.68	10.72	8.38	64.34	24 (23)
	Aqueous phase	**15**	0.44	0.26	1.32	0.16	0.66	1.63	0.11	5.23	1.2 (1.7)
		75	0.21	0.74	na	1.60	0.21	0.58	0.39	1.41	0.73 (0.56)
		135	0.93	0.30	0.44	1.04	0.12	na	0.25	0.88	0.57 (0.37)
		195	na	0.11	na	0.59	0.61	na	0.21	0.29	0.36 (0.23)
Upper Small Intestine	Total aspirate	**30**	2.10	347.90	2087.49	2.08	4.99	349.70	147.41	47.74	374 (708)
		60	4.25	83.57	54.99	47.27	11.00	46.21	46.49	24.65	40 (26)
		90	202.25	51.58	10.61	3.13	17.89	7.51	9.95	6.57	39 (68)
		120	5.08	2.57	12.05	2.81	na	1.85	10.54	141.74	25 (52)
		150	1.85	3.67	na	3.55	21.07	3.07	7.81	23.86	9.3 (9.2)
		180	283.04	1.62	13.70	21.03	5.75	1.32	4.69	5.10	42 (98)
		210	3.59	1.15	16.99	2.41	10.42	0.67	3.57	3.48	5.3 (5.6)
		240	2.03	0.96	7.11	16.64	1.71	0.85	3.93	2.98	4.5 (5.3)
	Micellar phase	**30**	0.56	na	8.76	1.92	4.27	9.37	na	na	5.0 (4.0)
		60	4.79	na	2.26	4.75	3.93	4.88	na	0.35	3.5 (1.8)
		90	32.44	na	0.38	0.19	na	0.07	na	0.06	7 (14)
		120	0.46	0.20	na	0.10	na	0.02	1.75	1.78	0.72 (0.82)
		150	0.94	na	na	0.11	na	0.05	na	1.19	0.57 (0.58)
		180	16.40	0.78	0.23	0.14	0.04	0.01	na	0.24	2.5 (6.1)
		210	0.71	na	na	0.04	na	0.33	na	0.03	0.28 (0.32)
		240	0.14	na	0.16	0.21	0.05	0.02	na	0.08	0.109 (0.074)

Table Ap.VI.4. Danazol data (μg/mL) after administration of aqueous danazol suspension (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	242.18	120.81	257.76	159.60	35.43	352.29	478.15	17.30	208 (157)
		75	93.34	76.91	100.34	96.88	137.13	na	95.46	8.60	87 (39)
		135	46.80	39.67	23.16	27.90	37.10	na	39.21	11.15	32 (12)
		195	65.61	16.87	14.20	5.82	na	na	9.83	21.85	22 (22)
	Aqueous phase	15	1.54	1.06	1.04	0.85	0.27	0.94	0.97	0.53	0.90 (0.38)
		75	1.15	1.72	0.26	0.55	0.25	na	1.49	0.28	0.82 (0.63)
		135	0.85	0.71	0.53	0.58	na	na	0.75	na	0.68 (0.13)
		195	0.46	0.19	na	0.22	na	na	na	0.25	0.28 (0.12)
Upper Small Intestine	Total aspirate	30	68.27	44.68	27.83	124.28	39.63	28.31	60.43	34.11	53 (32)
		60	20.54	31.83	10.20	47.33	32.43	50.71	22.46	19.04	29 (14)
		90	29.07	19.36	2.67	20.73	15.64	32.34	11.48	na	19 (10)
		120	7.14	21.60	7.49	46.24	3.50	33.19	7.80	na	18 (16)
		150	12.55	10.57	6.31	11.91	2.35	31.55	14.28	na	12.8 (9.2)
		180	5.99	10.28	3.61	6.57	3.40	9.28	2.11	na	5.9 (3.1)
		210	12.11	2.91	0.72	1.95	0.83	7.15	1.41	na	3.9 (4.3)
		240	1.89	6.56	0.52	1.02	0.61	9.90	1.02	na	3.1 (3.7)
	Micellar phase	30	9.00	na	na	0.24	6.97	9.42	na	na	6.4 (4.2)
		60	4.33	0.09	na	0.31	4.28	0.68	na	na	1.9 (2.2)
		90	1.14	0.07	na	0.12	2.33	0.13	na	na	0.8 (1.0)
		120	2.49	0.04	0.08	0.70	0.29	0.56	0.59	na	0.68 (0.84)
		150	1.18	na	na	0.03	na	0.35	0.26	na	0.45 (0.50)
		180	0.14	0.03	na	0.03	0.01	na	0.27	na	0.10 (0.11)
		210	0.23	1.08	na	0.04	0.23	1.95	0.36	na	0.64 (0.73)
		240	0.68	0.41	na	0.02	0.11	na	0.26	na	0.30 (0.26)

Table Ap.VI.5. Phenol red data (µg/mL) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	4.42	10.92	172.05	40.84	25.33	91.92	8.35	8.57	45 (59)
		75	19.19	87.21	177.52	72.17	17.30	134.61	110.09	48.29	83 (56)
		135	43.42	88.73	134.75	52.67	47.63	129.83	105.85	22.63	78 (42)
		195	35.09	51.76	74.65	29.29	74.90	82.77	78.57	30.12	57 (23)
	Aqueous phase	15	3.81	8.62	66.98	18.06	11.06	30.27	6.62	16.80	20 (21)
		75	13.99	35.65	na	30.88	11.39	39.98	29.74	19.15	26 (11)
		135	20.13	38.94	48.53	25.00	17.74	na	32.68	16.65	28 (12)
		195	na	35.79	na	22.51	28.45	na	21.82	16.44	25.0 (7.4)
Upper Small Intestine	Total aspirate	30	22.99	38.89	39.96	10.95	7.89	1.83	4.73	6.00	17 (15)
		60	23.87	38.93	101.94	62.13	23.15	49.12	22.40	10.41	41 (30)
		90	28.04	32.81	128.80	76.89	37.19	58.89	41.71	9.43	52 (37)
		120	59.64	32.52	64.85	88.66	26.91	75.12	45.20	4.83	50 (28)
		150	22.86	60.58	na	100.05	40.22	64.47	74.38	46.11	58 (25)
		180	17.68	31.03	36.88	41.43	59.77	47.42	86.45	78.61	50 (24)
		210	16.97	17.26	16.13	38.95	37.63	17.64	60.27	46.76	31 (17)
		240	14.58	16.63	10.93	25.77	31.10	30.07	30.54	24.60	23.0 (7.9)
	Micellar phase	30	18.89	na	39.59	10.45	7.09	2.08	na	na	16 (15)
		60	19.94	na	54.33	56.93	22.37	41.09	na	68.00	44 (19)
		90	24.45	na	60.93	70.20	na	38.84	na	58.83	51 (19)
		120	44.29	27.59	na	45.04	na	45.50	41.62	27.90	38.7 (8.56)
		150	19.53	na	na	58.29	na	27.36	na	22.28	32 (18)
		180	15.77	35.54	28.17	33.99	44.73	28.43	na	30.62	31.0 (8.8)
		210	14.40	na	na	31.31	na	16.57	na	33.87	24 (10)
		240	12.09	na	8.77	18.01	24.10	22.93	na	21.07	17.8 (6.2)

Table Ap.VI.6. Phenol red data (µg/mL) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	10.00	8.07	99.32	16.23	10.29	53.47	56.62	51.78	38 (33)
		75	38.02	90.75	64.39	58.89	57.35	na	85.62	17.04	59 (26)
		135	30.24	71.85	52.21	110.28	79.33	na	62.00	54.03	66 (25)
		195	24.67	40.65	35.34	44.90	na	na	92.82	25.05	44 (25)
	Aqueous phase	15	7.01	7.29	25.65	10.30	7.11	27.11	26.05	30.07	18 (10)
		75	19.52	31.68	27.49	14.63	12.67	na	26.20	18.72	21.6 (7.1)
		135	20.27	31.10	25.14	32.71	na	na	26.96	na	27.2 (4.9)
		195	17.97	28.72	na	16.55	na	na	na	10.36	18.4 (7.6)
Upper Small Intestine	Total aspirate	30	27.94	43.95	na	39.09	36.36	66.26	55.95	35.11	44 (13)
		60	32.39	79.68	72.64	43.34	39.86	117.46	76.67	65.64	66 (28)
		90	45.26	88.72	56.43	94.97	35.23	82.03	71.10	na	68 (23)
		120	18.96	70.36	54.33	52.98	28.32	81.05	50.97	na	51 (22)
		150	26.69	51.24	46.08	63.87	21.47	62.57	63.07	na	48 (18)
		180	20.91	42.80	38.06	15.76	32.37	36.93	40.04	na	32 (10)
		210	16.56	10.80	15.44	10.29	10.56	31.29	29.09	na	17.7 (8.9)
		240	6.83	6.25	9.24	7.38	3.34	32.53	19.95	na	12.2 (10.4)
	Micellar phase	30	29.68	na	na	33.05	42.90	53.37	na	na	40 (11)
		60	29.60	43.81	na	36.61	36.10	45.13	na	na	38.2 (6.3)
		90	38.36	46.88	na	45.52	32.40	42.91	na	na	41.2 (5.9)
		120	17.35	40.93	41.34	42.81	27.36	34.13	41.46	na	35.0 (9.6)
		150	25.46	na	na	37.47	na	31.16	40.70	na	33.7 (6.8)
		180	19.13	35.07	na	25.50	20.56	na	30.10	na	26.1 (6.6)
		210	15.69	13.37	na	10.20	9.44	28.40	26.53	na	17.3 (8.2)
		240	6.40	5.92	na	7.04	3.53	na	21.60	na	8.9 (7.2)

APPENDIX VII Data on sample volumes and physicochemical parameters characterizing the upper GI lumen contents

Table Ap.VII.1. Volume (mL) of aspirated antral contents and contents of the upper small intestine; and respective volume (mL) of aqueous/micellar phases after ultracentrifugation, after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	14.6	15.6	13.1	13.1	22.1	20.7	16.1	19.7	16.8 (3.5)
		75	15.6	16.6	5.6	16.6	18.0	18.5	15.5	18.0	15.6 (4.2)
		135	17.6	16.4	13.1	16.2	24.6	3.6	15.1	15.8	15.3 (5.8)
		195	8.6	15.4	0.6	16.6	18.6	9.2	13.1	16.2	12.3 (5.9)
		Total	56.4	64.0	32.4	62.5	83.3	52.0	59.8	69.7	60 (14)
	Aqueous phase	15	7.8	4.1	3.6	3.3	8.9	4.9	6.9	7.6	5.9 (2.2)
		75	4.8	2.8	na	4.8	9.4	3.8	5.6	9.4	5.8 (2.6)
		135	4.8	4.6	4.8	5.8	8.9	na	3.4	8.9	5.9 (2.2)
		195	na	4	2.8	8.8	7.4	na	6.9	4.4	5.7 (2.3)
Upper Small Intestine	Total aspirate	30	13.8	5.4	14.1	12.9	12.1	14.1	3.8	7.0	10.4 (4.3)
		60	18.6	3.4	13.1	14.8	14.6	16.5	0.6	7.0	11.1 (6.6)
		90	14.0	3.6	14.1	13.8	10.6	17.6	3.8	15.1	11.6 (5.2)
		120	13.6	12.2	0.6	15.8	0.2	16.7	15.3	15.2	11.2 (6.8)
		150	14.0	3.6	na	12.6	2.9	18.5	3.1	13.9	9.8 (6.4)
		180	14.6	13.4	13.6	15.8	12.6	15.3	2.6	15.6	12.9 (4.3)
		210	15.8	5.6	5.6	15.6	5.2	16.1	0.6	15.0	9.9 (6.3)
		240	13.6	3.6	16.6	17.1	16.2	19.7	3.2	14.6	13.1 (6.2)
		Total	118.0	50.8	77.7	118.4	74.4	134.5	33.0	103.4	88 (35)
	Micellar phase	30	8.3	na	na	9.8	6.2	6.2	na	na	7.6 (1.7)
		60	9.3	na	3.3	5.6	5.6	4.4	na	4.4	5.4 (2.1)
		90	8.8	na	2.6	5.8	na	3	na	7.5	5.5 (2.7)
		120	2	5.6	na	4.0	na	5.3	3.2	6.9	4.5 (1.8)
		150	8.8	na	na	4.8	na	6.4	na	9.4	7.3 (2.1)
		180	8.8	3.1	2.1	9.0	4.6	5	na	8.5	5.9 (2.9)
		210	8.8	na	na	9.8	na	6.2	na	9.4	8.5 (1.6)
		240	9.3	na	7.8	10.8	7.4	8.9	na	9.5	8.9 (1.2)

Table Ap.VII.2. Volume (mL) of aspirated antral contents and contents of the upper small intestine and respective volume (mL) of aqueous/micellar phases after ultracentrifugation, after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	17.6	16.6	18.6	19.6	19.6	16.6	25.6	24.6	19.8 (3.4)
		75	19.6	15.6	20.6	17.6	27.6	na	23.6	24.6	21.3 (4.2)
		135	20.6	18.6	19.6	15.6	0.6	na	22.6	7.0	14.9 (8.1)
		195	19.6	18.6	2.4	22.6	na	na	5.2	26.2	15.8 (9.7)
		Total	77.4	69.4	61.2	75.4	47.8	16.6	77	82.4	63 (21)
	Aqueous phase	15	5.8	3.8	9.0	7.8	9.4	4.5	9.4	9.0	7.3 (2.3)
		75	4.0	5.0	10.3	9.8	9.4	na	5.5	9.2	7.6 (2.6)
		135	3.0	2.8	10.3	8.6	na	na	5.3	na	6.0 (3.3)
		195	7.8	6.8	na	9.2	na	na	na	9.2	8.2 (1.2)
Upper Small Intestine	Total aspirate	30	18.6	4.2	0.2	17.6	16.6	11.6	4.4	7.0	10.02 (7.05)
		60	17.6	15.6	1.1	15.6	18.6	25.6	4.2	6.1	13.0 (8.4)
		90	17.6	15.6	1.1	17.6	22.6	24.6	0.6	na	14.2 (9.7)
		120	16.6	15.6	19.6	17.6	20.6	24.6	18.1	na	18.96 (3.01)
		150	19.6	4.8	1.4	18.6	8.4	21.6	18.1	na	13.2 (8.1)
		180	18.6	18.6	4.2	18.6	19.6	3.8	13.1	na	13.79 (7.02)
		210	15.1	16.6	3.1	19.6	19.6	14.6	17.1	na	15.1 (5.6)
		240	14.6	16.6	4.6	17.6	22.2	4.6	21.6	na	14.5 (7.3)
		Total	138.3	107.6	35.3	142.8	148.2	131.0	97.2	13.1	102 (51)
	Micellar phase	30	5.0	na	na	9.8	5.2	3.5	na	na	5.9 (2.7)
		60	7.8	5.8	na	9.4	8.2	8.9	na	na	8.0 (1.4)
		90	9.0	5.3	na	9.4	7.9	6.5	na	na	7.6 (1.7)
		120	9.0	5.8	9.8	5.1	9.2	7.6	7.4	na	7.7 (1.8)
		150	9.8	na	na	9.4	na	2.1	8.4	na	7.4 (3.6)
		180	10.3	4.6	na	9.4	9.0	na	3.8	na	7.42 (2.99)
		210	10.3	9.6	na	9.4	8.6	8.4	9.4	na	9.28 (0.69)
		240	10.3	4.3	na	9.4	9.0	na	8.9	na	8.4 (2.3)

Table Ap.VII.3. pH of antral contents and contents of the upper small intestine

GI Location	Study Phase	Time (min)	1	2	3	5	6	8	9	10	Median
Antrum	Phase I Solutions	15	2.2	1.7	6.5	2.1	6.2	3.8	3.1	2.6	2.9
		75	3.0	1.0	5.9	3.0	4.8	4.2	4.6	4.0	4.1
		135	2.1	1.4	4.6	2.8	4.2	3.9	4.1	2.2	3.4
		195	1.3	1.1	4.0	2.3	3.2	3.1	3.9	1.4	2.7
	Phase II Suspensions	15	2.1	1.73	5.25	2.53	2.55	4.3	4.7	5.54	3.4
		75	2.08	2.02	3.54	2.46	2.8	na	3.05	4.98	2.8
		135	1.55	1.58	2.6	3.8	2.9	na	2.95	4.04	2.9
		195	1.43	1.15	1.5	1.92	na	na	2.47	1.78	1.6
Upper Small Intestine	Phase I Solutions	30	6.1	6.4	6.2	7.3	6.7	6.8	6.6	5.8	6.5
		60	6.2	6.9	5.6	6.5	5.9	6.0	5.6	5.6	5.9
		90	6.4	6.7	5.3	6.3	4.6	6.9	4.7	5.2	5.8
		120	6.3	5.3	5.8	4.9	6.0	5.8	4.9	5.2	5.6
		150	4.5	6.1	6.3	5.3	3.9	5.1	3.6	5.9	5.2
		180	6.5	6.6	5.2	4.7	4.9	5.1	3.6	4.8	5.0
		210	7.2	6.1	5.5	4.6	4.0	5.6	6.5	4.3	5.5
		240	6.7	3.5	4.9	3.8	4.6	5.4	3.5	4.3	4.5
	Phase II Suspensions	30	6.44	6.31	7.47	4.91	6.26	6.08	6.16	6.38	6.3
		60	6.38	4.8	6.17	5.52	4.92	4.87	5.82	5.78	5.7
		90	5.48	4.85	5.87	5.08	5.41	5.07	5.73	na	5.4
		120	6.66	4.52	5.08	5.57	4.32	3.77	5.04	na	5.0
		150	5.6	4.17	6.06	4.57	6.35	3.31	4.46	na	4.6
		180	6.16	4.43	5.3	4.03	3.66	5.77	5.05	na	5.1
		210	6.23	6.6	7.74	2.59	4.85	5.7	5.26	na	5.7
		240	6.5	6.47	6.83	4.1	4.1	5.55	5.28	na	5.6

Table Ap.VII.4. Buffer capacity (mmol/L/ΔpH) of antral contents and contents of the upper small intestine

GI Location	Study Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Phase I Solutions	15	14.0	na	17.0	16.5	4.8	25.7	4.0	8.1	12.9 (7.8)
		75	45.0	na	28.0	22.7	4.7	25.8	23.2	16.9	23 (12)
		135	30.0	na	26.3	19.0	12.0	31.3	28	15.4	23.1 (7.6)
		195	47.0	na	na	17.0	22.0	3.08	24.8	36.0	25 (15)
	Phase II Suspensions	15	11.6	18.6	15.0	8.1	7.48	12.4	9.15	5.75	11.0 (4.3)
		75	18.0	23.3	17.0	14.3	14.3	na	21.8	8.05	16.7 (5.1)
		135	36.0	34.0	21.3	26.4	na	na	20.6	13.1	25.2 (8.7)
		195	28.0	53.0	33.0	21.5	na	na	22.9	21.5	30 (12)
Upper Small Intestine	Phase I Solutions	30	34.1	18.0	12.8	60.0	na	36.6	35.0	20.6	31 (16)
		60	48.0	21.5	24.0	17.0	11.0	18.1	na	28.9	24 (12)
		90	43.0	16.5	35.0	29.0	15.2	21.5	29.0	27.0	27.0 (9.3)
		120	21.0	na	na	20.0	na	23.2	21.4	15.4	20.2 (2.9)
		150	15.0	22.0	17.9	26.0	16.3	20.5	26.7	11.7	19.5 (5.3)
		180	30.0	na	na	17.0	26.8	15.4	27.1	13.8	21.68 (7.05)
		210	20.0	45.3	7.0	16.0	17.4	28.9	na	19.6	22 (12)
		240	10.0	17.0	7.0	13.8	16.6	18.6	16.9	28.7	16.1 (6.5)
	Phase II Suspensions	30	30.0	17.0	na	11.2	30.5	29.8	24.9	25.5	24.1 (7.4)
		60	na	24.0	na	13.0	20.2	23	20.9	25.2	21.1 (4.4)
		90	17.5	24.0	na	22.1	16.7	20.8	21.8	na	20.5 (2.8)
		120	52.0	23.0	17.0	18.6	16.9	24.6	20.8	na	25 (12)
		150	15.3	19.0	na	20.0	23	20.7	20.8	na	19.8 (2.6)
		180	23.0	17.0	17.0	13.2	15.4	11.6	17.5	na	16.4 (3.6)
		210	16.8	41.1	34.0	25.0	8.0	11.1	11.8	na	21 (13)
		240	24.0	20.0	13.6	5.3	14.1	8.85	17.8	na	14.8 (6.4)

Table Ap.VII.5. Osmolality (mOsm/kg) of aqueous/micellar phases of antral contents and contents of the upper small intestine

GI Location	Study Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Phase I Solutions	15	91	31	504	95	29	166	67	154	142 (155)
		75	220	327	na	317	131	391	365	242	284 (91)
		135	218	251	447	269	94	na	443	180	272 (131)
		195	na	289	na	na	265	na	353	199	277 (64)
	Phase II Suspensions	15	81	86	286	86	68	285	270	152	164 (99)
		75	274	307	307	235	90	na	402	24	234 (132)
		135	280	350	334	419	na	na	361	na	349 (50)
		195	263	282	na	na	na	na	na	166	237 (62)
Upper Small Intestine	Phase I Solutions	30	237	na	416	291	195	262	na	na	280 (84)
		60	309	na	397	375	76	308	na	481	324(138)
		90	381	na	561	391	na	346	na	417	419 (83)
		120	322	230	na	343	na	383	361	260	317 (60)
		150	307	na	na	316	na	281	na	267	293 (23)
		180	280	240	332	315	412	262	na	285	304 (57)
		210	221	na	na	295	na	220	na	286	256 (41)
		240	203	na	147	164	274	203	na	236	205 (46)
	Phase II Suspensions	30	301	na	na	286	395	340	na	na	331 (49)
		60	317	190	na	348	378	510	na	na	349 (115)
		90	359	459	377	446	143	429	na	na	369 (117)
		120	296	410	na	406	325	388	348	na	362 (47)
		150	314	na	na	395	na	348	351	na	352 (33)
		180	294	301	na	207	252	na	332	na	277 (49)
		210	143	196	na	213	224	229	109	na	186 (49)
		240	150	242	na	240	72	na	272	na	195 (83)

Table Ap.VII.6. Viscosity (mPa·s) of antral contents and contents of the upper small intestine after administration of drug solutions (Phase I)

GI Location	Time (min)	Shear rate (s^{-1})	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	15	50	49.2	52.6	na	na	1614.5	2605.9	59.7	32.3	736 (1110)
		100	26.3	20.6	na	na	1276.2	2070.0	20.0	14.0	572 (890)
		200	18.6	10.5	na	na	721.3	1179.5	10.4	9.8	325 (506)
	75	50	200.4	2427.6	2225.1	2686.7	105.7	2233.0	2554.0	2868.5	1913 (1107)
		100	84.6	1797.3	1719.8	1613.3	57.2	1596.2	1663.6	2340.0	1359 (830)
		200	51.1	998.5	1045.0	853.4	33.6	949.1	948.8	1290.5	771 (467)
	135	50	627.6	1814.4	na	1027.0	417.7	2189.3	3450.6	1196.3	1532 (1050)
		100	466.7	1315.2	na	539.2	228.2	1670.8	2249.1	953.4	1060 (728)
		200	222.4	733.2	na	221.5	129.8	1008.2	1136.0	589.6	557 (403)
	195	50	551.3	1035.9	na	37.0	1682.5	1067.7	na	585.0	827 (564)
		100	339.0	550.3	na	17.9	1053.4	771.7	na	364.5	516 (363)
		200	219.7	257.5	na	11.3	475.0	464.6	na	249.1	279 (173)
Upper Small Intestine	30	50	162.7	150.6	363.4	na	na	38.4	14.0	1454.8	364 (548)
		100	82.7	87.9	184.1	na	na	25.8	11.2	997.0	231 (280)
		200	47.3	60.0	126.8	na	na	22.1	11.6	584.9	142 (221)
	60	50	787.8	125.1	na	272.0	238.0	199.4	na	2164.0	361 (787)
		100	452.7	103.0	na	173.4	182.7	127.2	na	1715.1	459 (628)
		200	317.2	70.6	na	98.0	102.5	64.8	na	996.4	245 (366)
	90	50	406.2	37.7	1091.6	1650.7	240.0	1007.8	122.9	1913.7	809 (717)
		100	306.6	22.2	734.8	1200.1	113.2	432.7	64.4	1288.7	520 (503)
		200	201.4	15.6	443.9	750.5	59.7	232.9	53.4	746.8	313 (301)
	120	50	779.8	na	na	1475.5	na	1937.1	157.1	1344.2	1139 (687)
		100	798.9	na	na	1393.4	na	1197.6	160.4	701.6	850(479)
		200	465.9	na	na	824.4	na	695.2	66.5	482.0	507 (288)
	150	50	250.1	1301.7	na	na	322.1	942.3	1380.1	139.3	723 (555)
		100	102.9	829.4	na	na	154.1	485.1	795.9	84.4	409 (345)
		200	221.1	435.6	na	na	83.9	267.5	484.7	41.0	256 (180)
	180	50	109.5	594.7	53.6	336.5	na	387.5	1126.8	1884.8	642 (654)
		100	53.2	409.2	21.5	157.3	na	197.1	911.4	1112.6	409 (434)
		200	43.5	278.1	15.1	88.7	na	106.4	521.2	601.5	236 (238)
	210	50	16.6	17.4	36.1	754.8	158.4	5.7	na	1556.7	364 (591)
		100	9.1	8.5	15.4	475.5	65.1	3.6	na	748.6	189 (300)
		200	6.6	7.0	11.3	256.6	37.7	3.3	na	409.2	105 (163)
	240	50	18.6	73.3	68.1	599.0	215.0	1425.7	71.9	32.3	313 (489)
		100	9.2	40.6	31.6	309.5	120.0	709.4	49.4	14.5	161 (243)
		200	6.2	26.0	29.4	161.7	71.1	384.1	24.0	10.9	89 (129)

Table Ap.VII.7. Viscosity (mPa·s) of antral contents and contents of the upper small intestine after administration of drug suspensions (Phase II)

GI Location	Time (min)	Shear rate (s^{-1})	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	15	50	29.5	3.1	1842.9	8.8	519.8	1428.4	1340.2	1301.8	809 (752)
		100	15.5	1.8	1546.2	4.2	217.2	889.5	746.6	747.3	521 (557)
		200	9.2	2.0	907.8	4.0	107.2	535.8	389.7	423.9	297 (327)
	75	50	236.4	na	1226.3	1058.6	2288.8	na	1169.5	621.5	1100 (694)
		100	130.6	na	656.7	643.0	1713.8	na	878.4	290.6	719 (558)
		200	63.2	na	416.2	442.8	958.4	na	491.6	130.5	417 (318)
	135	50	332.4	734.4	2423.0	na	na	na	2518.7	2505.8	1703 (1078)
		100	115.6	316.8	1706.1	na	na	na	1851.5	1560.7	1110 (826)
		200	84.3	192.3	895.0	na	na	na	1063.9	919.6	631 (456)
	195	50	145.5	51.2	na	1583.3	na	na	2056.3	586.4	885 (893)
		100	64.1	22.5	na	1278.1	na	na	1379.1	387.6	626 (657)
		200	39.1	13.9	na	668.2	na	na	835.0	237.2	359 (374)
Upper Small Intestine	30	50	116.6	1473.2	na	263.0	92.8	na	102.1	41.8	348 (556)
		100	58.6	1429.5	na	118.5	45.0	na	67.5	21.9	290 (559)
		200	38.7	865.5	na	83.3	31.9	na	41.2	18.0	180 (337)
	60	50	69.3	na	na	98.3	191.8	2425.3	1042.6	1442.3	878 (946)
		100	28.7	na	na	41.2	76.9	1304.9	853.7	944.0	542 (561)
		200	22.1	na	na	24.0	38.1	678.0	526.0	429.6	286 (294)
	90	50	162.9	na	na	2008.4	310.9	396.4	na	na	720 (865)
		100	124.9	na	na	1397.5	173.0	196.6	na	na	473 (617)
		200	65.0	na	na	833.7	81.0	98.2	na	na	269 (376)
	120	50	16.9	na	228.9	133.3	48.9	1656.5	109.6	na	366 (637)
		100	8.4	na	121.7	87.2	25.5	1118.6	58.2	na	237 (434)
		200	8.3	na	71.6	53.8	14.9	659.2	31.2	na	140 (256)
	150	50	41.9	725.3	na	1472.5	618.5	971.9	1567.0	na	900 (570)
		100	22.0	463.2	na	919.0	257.9	562.1	826.4	na	508 (339)
		200	13.7	264.3	na	532.1	162.0	318.2	523.1	na	302 (203)
	180	50	11.2	42.9	226.9	40.2	376.6	233.6	75.5	na	144 (137)
		100	7.3	20.9	98.4	19.1	196.7	215.0	37.8	na	85 (88)
		200	5.8	15.4	56.6	13.4	127.7	106.3	27.0	na	50 (49)
	210	50	na	10.1	11.0	8.9	8.7	16.6	140.6	na	33 (53)
		100	na	6.6	7.6	4.1	4.1	8.2	69.5	na	17 (26)
		200	na	4.5	5.3	3.8	3.8	6.5	80.9	na	17 (31)
	240	50	na	9.3	23.1	10.8	59.7	42.9	153.6	na	50 (54)
		100	na	5.8	9.9	4.0	25.6	20.5	88.6	na	26 (32)
		200	na	5.9	6.9	3.0	13.8	14.0	56.5	na	17 (20)

APPENDIX VIII Data on solubilizing species concentrations in samples aspirated from the upper GI lumen

Table Ap.VIII.1: Taurocholic acid data (mM)

Study Phase	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Phase I Solutions	Total aspirate	30	0.43	1.02	0.22	na	2.02	na	3.34	1.79	1.5 (1.2)
		60	0.94	2.55	0.03	0.22	0.98	1.33	na	1.59	1.09 (0.85)
		90	0.73	1.01	na	0.22	0.75	0.56	1.51	1.08	0.83 (0.41)
		120	0.75	0.08	0.76	0.10	na	0.72	2.41	0.86	0.81 (0.78)
		150	0.55	0.99	0.55	na	0.41	0.79	1.65	0.98	0.85 (0.42)
		180	0.55	0.37	na	0.25	na	0.41	0.95	1.35	0.65 (0.42)
		210	0.43	1.07	0.14	0.07	0.39	1.00	na	0.85	0.5 (0.41)
		240	0.02	0.40	0.21	0.15	1.05	0.17	1.39	0.48	0.48 (0.48)
	Micellar phase	30	0.18	na	0.13	0.54	2.02	2.50	na	na	1.1 (1.1)
		60	0.94	na	0.10	0.19	0.59	1.11	na	0.49	0.57 (0.40)
		90	0.60	na	0.07	0.13	na	0.69	na	0.46	0.39 (0.28)
		120	0.38	0.37	na	0.05	na	0.58	1.79	0.50	0.61 (0.61)
		150	0.31	na	na	0.20	na	0.37	na	0.72	0.40 (0.22)
		180	0.37	1.29	0.30	0.10	0.54	0.24	na	0.74	0.51 (0.40)
		210	0.19	na	na	0.04	na	0.79	na	0.38	0.35 (0.33)
		240	0.03	na	0.24	0.15	0.69	0.35	na	0.25	0.29 (0.22)
Phase II Suspensions	Total aspirate	30	0.83	2.00	na	0.24	1.56	na	2.08	2.71	1.57 (0.90)
		60	0.75	na	1.09	0.44	1.24	na	2.08	2.18	1.3 (0.70)
		90	0.52	na	0.86	0.44	1.23	1.15	2.11	na	1.05 (0.61)
		120	0.81	na	0.36	0.51	0.50	0.16	0.41	na	0.46 (0.21)
		150	0.83	0.91	0.16	0.44	1.78	0.42	1.12	na	0.81 (0.54)
		180	0.18	0.47	0.77	0.29	0.29	1.76	1.60	na	0.76 (0.65)
		210	0.16	1.44	0.57	0.08	0.41	0.82	1.52	na	0.71 (0.58)
		240	0.22	0.38	0.29	0.01	0.63	0.64	0.93	na	0.44 (0.31)
	Micellar phase	30	0.86	na	na	0.15	1.63	1.44	na	na	1.02 (0.67)
		60	0.78	0.71	na	0.18	1.03	0.10	na	na	0.56 (0.40)
		90	0.54	0.47	na	0.22	0.86	0.49	na	na	0.51 (0.23)
		120	0.89	0.68	0.32	0.41	0.78	0.10	0.90	na	0.58 (0.31)
		150	0.71	na	na	0.20	na	0.09	0.98	na	0.50 (0.42)
		180	0.25	0.48	na	0.19	0.49	na	1.08	na	0.50 (0.35)
		210	0.20	1.28	na	0.05	0.33	0.97	1.43	na	0.71 (0.59)
		240	0.30	0.48	na	0.02	0.54	na	0.98	na	0.46 (0.35)

Table Ap.VIII.2: Glycocholic acid data (mM)

Study Phase	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Phase I Solutions	Total aspirate	30	1.67	2.79	1.55	na	7.05	na	7.77	2.76	3.9 (2.8)
		60	7.32	7.50	0.14	1.38	2.96	3.21	na	2.00	3.5 (2.9)
		90	4.21	3.23	na	1.33	2.59	1.66	2.59	1.82	2.5 (1.0)
		120	4.21	0.26	4.19	0.46	na	2.30	4.60	1.47	2.5 (1.8)
		150	2.54	4.05	3.12	na	1.55	2.33	3.29	1.56	2.63 (0.92)
		180	2.63	1.47	na	1.61	na	1.08	2.21	2.06	1.84 (0.56)
		210	1.64	3.10	0.94	0.42	1.58	2.50	na	1.64	1.69 (0.90)
		240	0.22	1.35	1.60	0.73	2.81	0.54	2.79	1.02	1.38 (0.98)
	Micellar phase	30	1.68	na	0.75	3.44	6.90	7.61	na	na	4.1 (3.1)
		60	7.91	na	0.13	1.22	1.77	2.83	na	0.68	2.4 (2.8)
		90	5.73	na	0.33	0.89	na	1.66	na	0.74	1.9 (2.2)
		120	2.93	1.54	na	0.23	na	1.69	3.53	0.81	1.8 (1.2)
		150	2.61	na	na	1.09	na	0.87	na	1.06	1.41 (0.81)
		180	2.91	3.31	1.51	0.56	1.30	0.56	na	1.13	1.6 (1.1)
		210	1.43	na	na	0.24	na	2.30	na	0.67	1.16 (0.91)
		240	0.19	na	0.49	0.65	1.43	0.88	na	0.54	0.70 (0.42)
Phase II Suspensions	Total aspirate	30	3.73	3.73	na	1.51	4.45	na	4.55	3.29	3.5 (1.1)
		60	3.11	na	4.43	2.55	3.52	na	3.53	2.17	3.22 (0.80)
		90	2.93	na	3.25	2.26	3.28	3.03	4.23	na	3.16 (0.64)
		120	3.59	na	1.88	2.77	1.93	0.58	1.30	na	2.0 (1.1)
		150	3.57	2.49	0.89	2.49	4.62	1.07	2.84	na	2.6 (1.3)
		180	1.01	1.06	3.72	1.81	1.10	4.33	3.47	na	2.4 (1.4)
		210	0.91	2.49	2.58	0.45	1.56	2.33	3.73	na	2.0 (1.1)
		240	1.19	0.88	1.39	0.14	2.03	1.56	2.31	na	1.36 (0.72)
	Micellar phase	30	3.78	na	na	0.83	4.32	3.31	na	na	3.1 (1.5)
		60	3.18	1.29	na	0.96	2.93	0.31	na	na	1.7 (1.3)
		90	3.00	0.92	na	1.02	2.31	1.20	na	na	1.69 (0.92)
		120	3.57	1.03	1.26	2.03	2.36	0.31	2.30	na	1.8 (1.1)
		150	2.56	na	na	0.93	na	0.25	2.15	na	1.5 (1.1)
		180	0.97	0.78	na	0.94	1.27	na	2.35	na	1.26 (0.63)
		210	0.89	2.65	na	0.28	1.22	2.31	3.52	na	1.8 (1.2)
		240	1.32	1.04	na	0.14	1.72	na	2.47	na	1.34 (0.86)

Table Ap.VIII.3: Taurochenodeoxycholic acid data (mM)

Study Phase	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Phase I Solutions	Total aspirate	30	0.30	1.18	0.41	na	2.92	na	2.72	1.46	1.5 (1.1)
		60	1.04	2.62	0.03	0.39	1.32	2.15	na	1.15	1.24 (0.91)
		90	0.74	1.02	na	0.43	0.79	0.87	1.28	0.85	0.85 (0.26)
		120	0.74	0.04	0.98	0.17	na	1.17	2.67	0.77	0.93 (0.87)
		150	0.18	1.05	0.73	na	0.57	1.21	1.76	0.90	0.92 (0.50)
		180	0.43	0.46	na	0.49	na	0.63	1.02	1.11	0.69 (0.30)
		210	0.26	1.03	0.17	0.12	0.56	1.45	na	0.68	0.61 (0.49)
		240	0.04	0.41	0.31	0.09	1.45	0.21	1.29	0.40	0.52 (0.54)
	Micellar phase	30	0.24	na	0.07	0.74	2.95	2.94	na	na	1.4 (1.4)
		60	1.01	na	0.05	0.19	0.81	1.17	na	0.18	0.57 (0.49)
		90	0.77	na	0.05	0.10	na	0.27	na	0.17	0.27 (0.29)
		120	0.34	0.34	na	0.03	na	0.27	1.37	0.24	0.43 (0.47)
		150	0.33	na	na	0.12	na	0.31	na	0.44	0.30 (0.13)
		180	0.43	1.12	0.10	0.06	0.16	0.12	na	0.29	0.33 (0.37)
		210	0.20	na	na	0.03	na	1.10	na	0.14	0.37 (0.49)
		240	na	na	0.06	0.07	0.31	0.11	na	0.11	0.13 (0.10)
Phase II Suspensions	Total aspirate	30	0.81	1.55	na	0.33	1.81	na	2.39	1.82	1.45 (0.75)
		60	0.75	na	1.14	0.61	1.75	na	2.22	1.66	1.36 (0.63)
		90	0.67	na	0.88	0.60	1.74	1.18	2.02	na	1.18 (0.59)
		120	0.91	na	0.51	0.64	0.73	0.20	0.45	na	0.57 (0.25)
		150	0.89	0.88	0.19	0.63	2.45	0.46	1.30	na	0.97 (0.74)
		180	0.21	0.42	1.17	0.44	0.33	1.96	1.74	na	0.90 (0.72)
		210	0.19	1.10	0.62	0.08	0.51	1.16	1.48	na	0.73 (0.53)
		240	0.24	0.30	0.30	0.02	0.67	0.71	0.91	na	0.45 (0.32)
	Micellar phase	30	0.88	na	na	0.06	2.36	1.65	na	na	1.2 (1.0)
		60	0.85	0.16	na	0.10	1.02	0.16	na	na	0.46 (0.44)
		90	0.44	0.11	na	0.09	0.85	0.21	na	na	0.34 (0.32)
		120	0.92	0.16	0.11	0.21	0.70	0.13	0.61	na	0.40 (0.33)
		150	0.66	na	na	0.08	na	0.12	0.52	na	0.35 (0.29)
		180	0.13	0.14	na	0.23	0.22	na	0.72	na	0.29 (0.25)
		210	0.14	1.07	na	0.04	0.35	0.98	1.23	na	0.64 (0.52)
		240	0.32	0.37	na	0.02	0.51	na	0.71	na	0.38 (0.25)

Table Ap.VIII.4: Ursodeoxycholic acid data (mM)

Study Phase	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Phase I Solutions	Total aspirate	30	0.12	0.95	5.38	na	0.35	na	1.15	0.68	1.4 (2.0)
		60	0.34	0.79	0.13	0.31	0.20	0.61	na	0.52	0.41 (0.24)
		90	1.00	0.23	na	0.20	0.12	0.27	0.31	0.41	0.36 (0.30)
		120	0.28	na	0.25	0.10	na	0.36	0.62	1.13	0.45 (0.37)
		150	0.16	0.27	0.17	na	0.12	0.38	0.40	0.40	0.27 (0.12)
		180	0.75	0.10	na	0.28	na	0.15	0.18	0.50	0.33 (0.25)
		210	0.10	0.18	0.12	0.06	0.11	0.39	na	0.38	0.19 (0.14)
		240	0.02	0.08	0.08	0.04	0.22	0.08	0.36	0.23	0.14 (0.12)
	Micellar phase	30	0.08	na	0.04	0.34	0.39	1.27	na	na	0.42 (0.50)
		60	0.38	na	0.07	0.16	0.08	0.41	na	0.08	0.20 (0.16)
		90	0.40	na	0.05	0.04	na	0.10	na	0.08	0.13 (0.15)
		120	0.13	0.10	na	0.00	na	0.10	0.41	0.11	0.14 (0.14)
		150	0.14	na	na	0.05	na	0.04	na	0.18	0.103 (0.064)
		180	0.20	0.32	0.01	0.02	0.02	0.03	na	0.13	0.10 (0.12)
		210	0.07	na	na	na	na	0.38	na	0.08	0.18 (0.18)
		240	na	na	0.04	0.03	0.03	0.05	na	0.07	0.045 (0.018)
Phase II Suspensions	Total aspirate	30	0.47	0.40	na	na	0.68	na	0.67	2.64	0.97 (0.94)
		60	0.32	na	0.32	0.17	0.60	na	0.47	2.08	0.66 (0.71)
		90	0.41	na	0.18	0.21	0.51	0.34	0.56	na	0.37 (0.16)
		120	0.42	na	0.15	0.31	0.25	0.14	0.07	na	0.23 (0.13)
		150	0.42	0.25	0.04	0.24	0.65	0.19	0.28	na	0.30 (0.19)
		180	0.08	0.09	0.21	0.18	0.10	0.49	0.36	na	0.22 (0.16)
		210	0.08	0.18	0.18	0.03	0.19	0.03	0.34	na	0.15 (0.11)
		240	0.09	0.10	0.08	na	0.23	0.15	0.21	na	0.143 (0.063)
	Micellar phase	30	0.38	na	na	0.01	0.80	0.42	na	na	0.40 (0.32)
		60	0.25	0.02	na	0.02	0.45	0.01	na	na	0.15 (0.20)
		90	0.23	0.02	na	0.02	0.30	0.04	na	na	0.12 (0.13)
		120	0.51	0.02	0.02	0.08	0.24	na	0.14	na	0.17 (0.19)
		150	0.33	na	na	0.01	na	na	0.11	na	0.15 (0.16)
		180	0.05	0.03	na	0.08	0.08	na	0.15	na	0.080 (0.047)
		210	0.07	0.22	na	na	0.12	0.27	0.32	na	0.20 (0.10)
		240	0.15	0.09	na	0.02	0.17	na	0.18	na	0.122 (0.067)

Table Ap.VIII.5: Glycochenodeoxycholic acid data (mM)

Study Phase	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Phase I Solutions	Total aspirate	30	2.13	3.04	1.95	na	9.69	na	7.10	3.14	4.5 (3.2)
		60	7.52	7.23	0.16	1.86	4.34	4.76	na	2.16	4.0 (2.8)
		90	5.16	2.98	na	1.89	2.67	2.50	2.66	1.82	2.8 (1.1)
		120	5.69	0.21	5.26	0.65	na	3.02	4.96	1.65	3.1 (2.3)
		150	3.00	3.87	3.92	na	2.12	3.10	3.51	1.89	3.06 (0.80)
		180	3.23	1.48	na	2.56	na	1.58	1.89	2.24	2.16 (0.66)
		210	2.02	2.95	0.13	0.62	2.01	3.31	na	1.78	1.8 (1.1)
		240	0.21	1.17	1.63	0.33	4.70	0.52	2.87	1.08	1.6 (1.5)
	Micellar phase	30	1.47	na	0.36	3.75	9.53	9.20	na	na	4.9 (4.3)
		60	7.37	na	0.07	0.97	2.16	3.33	na	0.24	2.4 (2.7)
		90	5.64	na	0.12	0.53	na	0.73	na	0.25	1.5 (2.4)
		120	2.28	1.27	na	0.09	na	0.70	2.70	0.36	1.2 (1.1)
		150	2.38	na	na	0.69	na	0.78	na	0.69	1.14 (0.83)
		180	3.19	2.70	0.46	0.22	0.33	0.30	na	0.41	1.1 (1.3)
		210	1.50	na	na	0.12	na	3.15	na	0.22	1.2 (1.4)
		240	0.07	na	0.39	0.20	0.71	0.18	na	0.20	0.29 (0.23)
Phase II Suspensions	Total aspirate	30	3.31	3.27	na	na	5.32	na	5.03	2.37	3.9 (1.3)
		60	2.93	na	5.03	3.31	5.16	na	3.95	1.90	3.7 (1.3)
		90	3.18	na	3.67	3.07	4.83	3.64	3.90	na	3.71 (0.63)
		120	3.49	na	2.53	3.30	2.74	0.69	1.18	na	2.3 (1.1)
		150	3.49	2.15	0.96	3.59	6.66	1.47	2.66	na	3.0 (1.9)
		180	0.79	0.83	4.08	2.29	1.25	5.56	3.70	na	2.6 (1.8)
		210	0.84	2.09	3.92	0.42	2.05	2.27	3.33	na	2.1 (1.2)
		240	1.11	0.65	1.57	0.17	2.27	1.30	2.51	na	1.37 (0.83)
	Micellar phase	30	3.26	na	na	0.25	6.21	3.70	na	na	3.4 (2.4)
		60	2.87	0.26	na	0.33	3.68	0.35	na	na	1.5 (1.6)
		90	1.89	0.20	na	0.38	2.90	0.40	na	na	1.2 (1.2)
		120	3.64	0.22	0.40	0.95	2.60	0.26	1.49	na	1.4 (1.3)
		150	2.31	na	na	0.34	na	0.26	1.07	na	0.99 (0.95)
		180	0.43	0.23	na	0.72	0.68	na	1.59	na	0.73 (0.52)
		210	0.52	2.22	na	0.14	1.44	2.00	3.07	na	1.6 (1.1)
		240	1.20	0.77	na	0.07	1.79	na	1.86	na	1.14 (0.74)

Table Ap.VIII.6: Glycodeoxycholic acid data (mM)

Study Phase	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Phase I Solutions	Total aspirate	30	1.21	0.85	0.71	na	1.92	na	2.04	1.57	1.39 (0.55)
		60	4.17	1.92	na	1.44	0.87	1.88	na	1.12	1.9 (1.2)
		90	3.08	0.99	na	1.29	0.56	1.18	0.65	1.02	1.25 (0.85)
		120	3.39	0.03	1.59	0.51	na	1.65	1.49	0.84	1.4 (1.1)
		150	1.64	1.31	1.19	na	0.47	1.44	1.02	0.81	1.13 (0.40)
		180	1.79	0.37	na	1.95	na	0.59	0.52	1.06	1.05 (0.68)
		210	1.07	0.64	0.30	0.43	0.54	1.27	na	1.05	0.76 (0.37)
		240	0.12	0.31	0.49	0.19	na	0.24	0.74	0.69	0.40 (0.25)
	Micellar phase	30	0.92	na	0.09	2.53	1.99	4.42	na	να	2.0 (1.7)
		60	4.44	na	na	0.74	0.40	1.20	na	0.17	1.4 (1.8)
		90	3.93	na	0.05	0.37	na	0.28	na	0.16	1.0 (1.7)
		120	1.35	0.37	na	0.06	na	0.29	0.89	0.21	0.53 (0.49)
		150	1.35	na	na	0.52	na	0.13	na	0.33	0.58 (0.54)
		180	1.72	0.52	0.10	0.13	0.06	0.09	na	0.23	0.41 (0.60)
		210	0.83	na	na	0.07	na	0.17	na	0.16	0.31 (0.35)
		240	na	na	0.13	0.11	0.13	0.10	na	0.16	0.13 (0.02)
Phase II Suspensions	Total aspirate	30	2.14	0.71	na	na	2.62	na	1.51	1.20	1.64 (0.75)
		60	1.54	na	2.05	1.70	2.23	na	0.85	0.69	1.51 (0.62)
		90	2.60	na	1.30	1.42	1.96	0.90	1.06	na	1.54 (0.63)
		120	2.40	na	0.92	1.56	1.59	0.25	0.33	na	1.18 (0.83)
		150	2.34	0.48	0.24	1.89	2.72	0.43	0.93	na	1.3 (1.0)
		180	0.40	0.28	1.59	1.13	0.54	1.43	0.97	na	0.91 (0.51)
		210	0.48	0.43	1.58	0.22	1.14	0.70	0.91	na	0.78 (0.47)
		240	0.66	0.10	0.64	0.09	1.04	0.42	0.71	na	0.52 (0.34)
	Micellar phase	30	3.45	na	na	0.12	2.68	1.13	na	na	1.8 (1.5)
		60	1.55	0.05	na	0.16	1.62	0.12	na	na	0.70 (0.81)
		90	1.42	0.07	na	0.12	1.13	0.10	na	na	0.57 (0.66)
		120	2.30	0.04	0.11	0.42	1.26	0.05	0.46	na	0.66 (0.84)
		150	1.60	na	na	0.12	na	0.03	0.28	na	0.51 (0.74)
		180	0.26	0.05	na	0.30	0.23	nα	0.44	na	0.26 (0.14)
		210	0.34	0.39	na	0.06	0.70	0.58	0.95	na	0.50 (0.31)
		240	0.86	0.19	na	0.05	0.93	na	0.57	na	0.52 (0.39)

Table Ap.VIII.7: Total bile acids data (mM)

Study Phase	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Phase I Solutions	Total aspirate	30	5.86	9.84	10.21	na	23.94	na	24.12	11.41	14.2 (7.8)
		60	21.33	22.60	0.52	5.61	10.68	13.94	na	8.53	11.9 (8.1)
		90	14.91	9.46	na	na	7.47	7.04	9.00	6.99	9.1 (3.0)
		120	15.06	0.62	13.03	2.00	na	9.22	16.75	6.72	9.1 (6.3)
		150	8.08	11.55	9.68	na	5.24	9.26	11.62	6.54	8.9 (2.4)
		180	9.39	4.25	na	7.13	na	4.43	6.78	8.32	6.7 (2.1)
		210	5.54	8.98	1.80	1.72	5.20	9.93	na	6.38	5.6 (3.2)
		240	0.63	3.71	4.31	1.52	11.21	1.77	9.44	3.90	4.6 (3.8)
	Micellar phase	30	4.57	na	1.43	11.34	23.77	27.93	na	na	14 (12)
		60	22.06	na	0.42	3.47	5.81	10.06	na	1.84	7.3 (8.0)
		90	17.08	na	0.68	2.05	na	3.73	na	1.88	5.1 (6.8)
		120	7.41	3.99	na	0.46	na	3.63	10.70	2.25	4.7 (3.7)
		150	7.13	na	na	2.69	na	2.50	na	3.42	3.9 (2.2)
		180	8.82	9.26	2.48	1.10	2.41	1.35	na	2.93	4.0 (3.5)
		210	4.22	na	na	0.50	na	7.90	na	1.65	3.6 (3.3)
		240	0.30	na	1.36	1.21	3.30	1.67	na	1.34	1.53 (0.98)
Phase II Suspensions	Total aspirate	30	11.28	11.66	na	2.08	16.44	na	16.24	14.05	12.0 (5.3)
		60	9.41	na	14.06	8.77	14.50	na	13.12	10.68	11.8 (2.5)
		90	10.32	na	10.14	8.00	13.55	10.24	13.88	na	11.0 (2.3)
		120	11.64	na	6.34	9.09	7.75	2.02	3.75	na	6.8 (3.5)
		150	11.54	7.17	2.48	9.28	18.88	4.04	9.14	na	8.9 (5.4)
		180	2.65	3.15	11.55	6.13	3.62	15.53	11.83	na	7.8 (5.1)
		210	2.65	7.74	9.45	1.28	5.85	7.30	11.30	na	6.5 (3.6)
		240	3.51	2.41	4.26	0.46	6.87	4.78	7.58	na	4.3 (2.5)
	Micellar phase	30	12.61	na	na	1.42	17.99	11.66	na	na	10.9 (6.9)
		60	9.47	2.49	na	1.75	10.73	1.05	na	na	5.1 (4.6)
		90	7.52	1.79	na	1.85	8.35	2.43	na	na	4.4 (3.3)
		120	11.82	2.15	2.22	4.11	7.93	0.84	5.89	na	5.0 (3.9)
		150	8.17	na	na	1.68	na	0.75	5.12	na	3.9 (3.4)
		180	2.09	1.72	na	2.45	2.97	na	6.33	na	3.1 (1.9)
		210	2.16	7.84	na	0.58	4.15	7.12	10.52	na	5.4 (3.8)
		240	4.16	2.94	na	0.32	5.65	na	6.76	na	4.0 (2.5)

Table Ap.VIII.8: Linoleic acid data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.01	<LOQ	0.90	0.25	2.39	1.59	<LOQ	0.38	0.69 (0.88)
		75	0.04	0.67	2.03	1.10	0.69	1.30	2.01	1.25	1.14 (0.68)
		135	0.20	0.64	2.40	0.76	1.49	0.99	1.40	0.58	1.06 (0.69)
		195	0.30	0.42	na	0.28	2.31	1.26	na	0.09	0.78 (0.86)
	Aqueous phase	15	<LOQ	0.02	0.24	0.04	na	0.41	<LOQ	<LOQ	0.10 (0.16)
		75	<LOQ	0.17	na	0.24	<LOQ	0.10	0.06	<LOQ	0.08 (0.10)
		135	0.02	0.19	0.05	0.13	<LOQ	na	0.18	<LOQ	0.081 (0.084)
		195	na	0.08	na	0.07	0.02	na	<LOQ	<LOQ	0.036 (0.039)
Upper Small Intestine	Total aspirate	30	2.22	20.51	18.31	na	na	na	22.14	1.93	13 (10)
		60	4.75	9.59	2.62	9.29	4.11	6.15	na	3.97	5.8 (2.7)
		90	13.84	3.24	na	4.87	3.19	3.80	3.30	1.36	4.8 (4.1)
		120	5.10	na	na	2.36	na	3.88	9.46	7.00	5.6 (2.8)
		150	2.12	2.73	na	na	1.90	1.39	4.09	2.88	2.52 (0.94)
		180	15.89	1.85	3.65	2.74	na	0.62	7.12	2.60	4.9 (5.2)
		210	1.97	1.12	1.48	1.51	1.87	2.14	na	3.33	1.92 (0.71)
		240	0.47	8.01	1.38	0.97	2.02	0.57	3.59	2.65	2.5 (2.5)
	Micellar phase	30	1.11	na	0.43	2.19	3.48	16.56	na	na	4.8 (6.7)
		60	3.52	na	0.62	0.81	0.96	2.04	na	0.13	1.3 (1.2)
		90	1.15	na	0.19	0.34	na	0.76	na	0.12	0.51 (0.43)
		120	0.94	0.60	na	0.21	na	0.46	1.80	0.53	0.75 (0.56)
		150	0.85	na	na	0.36	na	<LOQ	na	0.43	0.41 (0.35)
		180	1.74	1.10	0.01	0.05	0.14	<LOQ	na	0.61	0.52 (0.67)
		210	0.33	na	na	0.10	na	1.91	na	0.03	0.59 (0.89)
		240	<LOQ	na	<LOQ	0.04	0.35	<LOQ	na	0.13	0.09 (0.14)

Table Ap.VIII.9: Linoleic acid data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.08	0.05	3.05	0.17	<LOQ	1.80	1.32	2.68	1.1 (1.3)
		75	0.41	na	4.05	0.59	1.11	na	0.95	0.56	1.3 (1.4)
		135	0.34	0.69	3.48	na	na	na	2.28	1.14	1.6 (1.3)
		195	0.48	0.56	1.43	0.64	na	na	1.62	0.65	0.89 (0.50)
	Aqueous phase	15	0.12	0.05	0.04	0.03	<LOQ	0.02	0.02	0.03	0.039 (0.036)
		75	0.31	0.17	0.03	0.04	0.04	na	0.08	<LOQ	0.10 (0.11)
		135	0.28	0.25	0.07	0.03	na	na	0.07	na	0.14 (0.12)
		195	0.02	0.06	na	0.04	na	na	na	<LOQ	0.029 (0.027)
Upper Small Intestine	Total aspirate	30	7.90	7.78	na	6.23	7.63	na	14.20	9.51	8.9 (2.8)
		60	7.20	na	5.33	na	3.77	10.77	14.77	12.88	9.1 (4.4)
		90	7.53	na	6.24	10.63	9.09	7.03	7.15	na	7.9 (1.6)
		120	7.25	na	5.34	6.41	na	3.31	4.15	na	5.3 (1.6)
		150	6.48	4.29	8.16	8.41	7.81	1.74	8.56	na	6.5 (2.6)
		180	3.83	3.08	3.64	3.74	na	4.97	7.25	na	4.4 (1.5)
		210	2.85	2.50	2.23	1.17	na	3.00	4.52	na	2.7 (1.1)
		240	1.60	2.12	1.39	0.30	1.37	1.67	2.08	na	1.50 (0.61)
	Micellar phase	30	4.47	na	na	<LOQ	4.69	4.72	na	na	3.5 (2.3)
		60	3.40	0.30	na	0.12	1.98	0.21	na	na	1.2 (1.5)
		90	0.80	0.23	na	0.40	2.48	0.30	na	na	0.84 (0.94)
		120	2.83	0.22	<LOQ	0.45	1.42	0.13	1.42	na	0.9 (1.0)
		150	1.68	na	na	<LOQ	na	0.18	0.72	na	0.65 (0.76)
		180	0.08	0.18	na	0.20	<LOQ	na	0.98	na	0.29 (0.40)
		210	0.04	1.55	na	0.22	0.62	1.23	2.36	na	1.00 (0.88)
		240	0.75	0.52	na	0.72	0.90	na	1.16	na	0.81 (0.24)

Table Ap.VIII.10: Oleic acid data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.04	0.15	1.33	0.56	2.36	3.65	0.23	0.44	1.1 (1.3)
		75	0.36	2.17	3.98	2.10	0.94	4.39	<LOQ	2.32	2.0 (1.6)
		135	0.91	2.07	5.56	1.91	1.93	3.83	<LOQ	1.36	2.2 (1.7)
		195	1.06	1.32	na	0.86	2.73	3.51	na	0.44	1.7 (1.2)
	Aqueous phase	15	0.01	0.04	0.88	0.08	na	0.25	na	0.02	0.21 (0.34)
		75	0.02	0.44	na	0.34	<LOQ	0.12	0.02	<LOQ	0.13 (0.18)
		135	0.10	0.30	0.09	0.16	<LOQ	na	0.19	<LOQ	0.12 (0.11)
		195	na	0.10	na	na	0.07	na	0.17	<LOQ	0.085 (0.070)
Upper Small Intestine	Total aspirate	30	4.49	9.01	8.43	na	na	na	4.12	3.99	6.0 (2.5)
		60	4.94	4.92	6.49	12.00	5.34	10.47	na	6.64	7.3 (2.8)
		90	0.47	8.39	na	11.81	6.25	10.10	5.19	4.09	6.6 (3.8)
		120	9.61	na	na	6.74	na	9.81	12.32	8.38	9.4 (2.1)
		150	3.67	8.89	na	na	3.96	4.33	12.11	5.20	6.4 (3.4)
		180	8.08	6.05	5.34	6.03	na	2.65	na	6.14	5.7 (1.8)
		210	2.83	2.56	1.80	3.54	4.65	3.41	na	6.12	3.6 (1.4)
		240	1.16	1.52	1.33	1.97	4.30	2.11	8.08	4.48	3.1 (2.4)
	Micellar phase	30	1.58	na	0.56	2.49	1.74	6.25	na	na	2.5 (2.2)
		60	3.33	na	1.39	1.53	1.39	1.81	na	0.25	1.6 (1.0)
		90	3.28	na	0.70	0.68	na	0.62	na	0.23	1.1 (1.2)
		120	1.85	0.78	na	0.05	na	0.15	2.49	0.69	1.0 (1.0)
		150	1.49	na	na	0.71	na	<LOQ	na	0.30	0.63 (0.65)
		180	1.99	1.77	0.98	0.08	0.25	<LOQ	na	0.54	0.80 (0.81)
		210	0.56	na	na	0.25	na	2.54	na	0.05	0.8 (1.1)
		240	<LOQ	na	0.06	<LOQ	0.50	<LOQ	na	0.13	0.12 (0.19)

Table Ap.VIII.11: Oleic acid data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.22	0.12	5.28	0.39	0.26	4.43	3.14	2.71	2.1 (2.1)
		75	0.43	na	4.21	1.74	3.47	na	3.85	1.44	2.5 (1.5)
		135	0.39	0.70	3.47	na	na	na	na	3.48	2.0 (1.7)
		195	0.52	0.52	2.25	2.10	na	na	5.15	1.84	2.1 (1.7)
	Aqueous phase	15	0.07	0.05	0.08	0.05	<LOQ	0.02	0.06	0.10	0.054 (0.030)
		75	0.07	0.24	0.05	0.05	0.06	na	0.18	<LOQ	0.092 (0.083)
		135	0.10	0.15	0.11	0.35	na	na	0.21	na	0.18 (0.11)
		195	0.05	0.04	na	0.06	na	na	na	<LOQ	0.036 (0.025)
Upper Small Intestine	Total aspirate	30	7.93	9.38	na	8.33	6.87	na	14.28	11.24	9.7 (2.7)
		60	7.94	na	1.68	na	3.47	na	15.48	16.49	9.0 (6.8)
		90	7.81	na	0.28	13.51	na	5.60	7.57	na	7.0 (4.8)
		120	7.17	na	0.97	8.89	na	8.46	4.63	na	6.0 (3.3)
		150	6.28	6.11	8.69	11.10	8.16	4.19	10.43	na	7.9 (2.5)
		180	4.63	2.86	3.92	5.19	na	5.77	8.49	na	5.1 (1.9)
		210	3.36	2.57	1.50	0.45	na	3.34	4.55	na	2.6 (1.5)
		240	1.28	2.51	1.50	0.38	0.92	2.67	2.46	na	1.67 (0.89)
	Micellar phase	30	3.00	na	na	<LOQ	5.11	6.87	na	na	3.7 (3.0)
		60	2.05	0.29	na	0.20	2.45	0.36	na	na	1.1 (1.1)
		90	1.08	0.23	na	0.56	2.27	0.25	na	na	0.88 (0.85)
		120	2.80	0.23	<LOQ	0.58	2.23	0.21	1.47	na	1.1 (1.1)
		150	1.93	na	na	<LOQ	na	0.24	0.79	na	0.74 (0.86)
		180	2.46	0.22	na	0.54	0.02	na	1.18	na	0.89 (0.99)
		210	1.19	1.45	na	0.21	0.67	1.29	2.32	na	1.19 (0.72)
		240	0.63	0.37	na	1.31	0.42	na	1.35	na	0.82 (0.48)

Table Ap.VIII.12: Stearic acid data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.01	<LOQ	0.45	0.14	0.34	0.73	0.07	0.22	0.24 (0.25)
		75	0.06	0.40	0.94	0.59	0.15	0.96	1.37	0.49	0.62 (0.44)
		135	0.17	0.38	1.23	0.51	0.37	1.08	1.13	0.29	0.64 (0.43)
		195	0.29	0.25	na	0.22	0.62	0.75	na	0.11	0.37 (0.25)
	Aqueous phase	15	0.01	0.02	0.15	0.02	na	0.07	0.02	0.02	0.044 (0.051)
		75	0.03	0.08	na	0.06	0.04	0.04	0.04	0.01	0.043 (0.023)
		135	0.04	0.06	0.05	0.05	0.01	na	0.09	0.01	0.043 (0.031)
		195	na	0.04	na	0.04	0.02	na	0.02	<LOQ	0.023 (0.017)
Upper Small Intestine	Total aspirate	30	1.27	5.10	5.20	na	na	10.34	4.97	3.52	5.1 (3.0)
		60	1.16	3.31	1.82	3.56	1.56	3.09	na	6.40	3.0 (1.8)
		90	7.89	2.10	na	4.39	1.91	3.20	2.81	4.65	3.9 (2.1)
		120	2.45	na	na	2.38	na	3.12	4.23	2.76	2.99 (0.75)
		150	0.86	2.26	na	na	1.15	1.23	3.54	1.48	1.8 (1.0)
		180	6.56	1.50	1.85	1.56	na	0.75	3.31	1.89	2.5 (2.0)
		210	0.76	0.66	0.56	0.81	1.38	1.10	na	1.75	1.00 (0.43)
		240	0.30	0.43	0.26	0.45	1.28	0.61	2.95	1.24	0.94 (0.90)
	Micellar phase	30	0.22	na	0.26	0.24	0.54	0.95	na	na	0.44 (0.31)
		60	0.65	na	0.30	0.24	0.59	0.59	na	0.37	0.46 (0.17)
		90	0.50	na	0.11	0.11	na	0.41	na	0.26	0.28 (0.18)
		120	0.35	0.08	na	0.10	na	0.34	0.68	0.29	0.30 (0.22)
		150	0.19	na	na	0.15	na	0.13	na	0.17	0.158 (0.028)
		180	0.27	0.38	0.13	0.11	0.07	0.16	na	0.33	0.21 (0.12)
		210	0.16	na	na	0.16	na	0.23	na	0.45	0.25 (0.14)
		240	0.29	na	0.03	0.13	0.09	0.12	na	0.39	0.17 (0.13)

Table Ap.VIII.13: Stearic acid data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.04	0.02	0.89	0.16	0.11	1.08	0.61	0.61	0.44 (0.41)
		75	0.23	na	0.93	0.40	0.64	na	0.80	0.35	0.56 (0.27)
		135	0.18	0.32	0.82	na	na	na	0.73	0.75	0.56 (0.29)
		195	0.27	0.23	0.54	0.44	na	na	0.92	0.45	0.48 (0.25)
	Aqueous phase	15	0.02	0.02	0.03	0.03	0.02	0.02	0.02	0.03	0.0228 (0.0058)
		75	0.06	0.08	0.03	0.02	0.03	na	0.05	0.02	0.042 (0.022)
		135	0.05	0.10	0.04	0.10	na	na	0.07	na	0.074 (0.028)
		195	0.06	0.03	na	0.03	na	na	na	<LOQ	0.030 (0.021)
Upper Small Intestine	Total aspirate	30	2.42	2.70	na	2.76	3.65	na	4.33	3.24	3.18 (0.71)
		60	2.31	na	4.74	na	3.48	3.76	4.55	5.56	4.1 (1.1)
		90	2.61	na	5.31	4.51	3.33	5.15	3.56	na	4.1 (1.1)
		120	2.09	na	3.49	2.89	na	1.93	2.67	na	2.61 (0.63)
		150	1.77	1.30	2.56	3.65	2.20	1.06	2.67	na	2.17 (0.89)
		180	1.55	2.28	0.92	1.45	na	1.71	1.93	na	1.64 (0.46)
		210	1.17	1.38	0.14	0.39	na	1.03	1.09	na	0.87 (0.49)
		240	0.46	0.80	0.30	0.07	0.22	0.86	0.73	na	0.49 (0.31)
	Micellar phase	30	0.68	na	na	0.03	1.68	1.75	na	na	1.03 (0.83)
		60	0.56	0.32	na	0.10	0.70	0.12	na	na	0.36 (0.26)
		90	0.24	0.16	na	0.19	0.45	0.42	na	na	0.29 (0.14)
		120	0.46	0.19	0.02	0.14	0.33	0.43	0.50	na	0.30 (0.18)
		150	0.35	na	na	0.02	na	0.36	0.22	na	0.24 (0.16)
		180	<LOQ	0.18	na	0.14	0.23	na	0.38	na	0.19 (0.14)
		210	<LOQ	0.26	na	0.10	0.11	0.24	0.45	na	0.19 (0.16)
		240	0.17	0.12	na	0.19	0.08	na	0.40	na	0.19 (0.12)

Table Ap.VIII.14: Total fatty acids data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.06	0.15	2.68	0.95	5.09	5.97	0.30	1.04	2.0 (2.3)
		75	0.45	3.25	6.95	3.79	1.79	6.65	3.38	4.06	3.8 (2.2)
		135	1.27	3.09	9.18	3.17	3.79	5.90	2.53	2.23	3.9 (2.5)
		195	1.66	1.99	na	1.36	5.66	5.52	na	0.64	2.8 (2.2)
	Aqueous phase	15	0.03	0.07	1.27	0.14	na	0.73	0.02	0.05	0.33 (0.49)
		75	0.05	0.69	na	0.64	0.04	0.27	0.12	0.01	0.26 (0.29)
		135	0.16	0.56	0.19	0.33	0.01	na	0.46	0.01	0.24 (0.21)
		195	na	0.22	na	0.11	0.11	na	0.19	<LOQ	0.127 (0.084)
Upper Small Intestine	Total aspirate	30	7.98	34.62	31.94	na	na	10.34	31.22	9.44	21 (13)
		60	10.84	17.82	10.92	24.85	11.00	19.71	na	17.02	16.0 (5.4)
		90	22.19	13.72	na	21.08	11.36	17.10	11.30	10.10	15.3 (4.9)
		120	17.16	na	na	11.48	na	16.82	26.01	18.14	17.9 (5.2)
		150	6.64	13.88	na	na	7.01	6.95	19.74	9.55	10.6 (5.2)
		180	30.53	9.40	10.84	10.33	na	4.01	10.43	10.63	12.3 (8.4)
		210	5.55	4.35	3.84	5.86	7.90	6.66	na	11.19	6.5 (2.5)
		240	1.94	9.97	2.97	3.38	7.60	3.29	14.62	8.37	6.5 (4.4)
	Micellar phase	30	2.92	na	1.24	4.93	5.76	23.76	na	na	7.7 (9.1)
		60	7.50	na	2.31	2.59	2.94	4.44	na	0.75	3.4 (2.3)
		90	4.93	na	1.00	1.13	na	1.79	na	0.61	1.9 (1.8)
		120	3.13	1.46	na	0.37	na	0.94	4.96	1.51	2.1 (1.7)
		150	2.53	na	na	1.22	na	0.13	na	0.90	1.2 (1.0)
		180	3.99	3.25	1.12	0.24	0.46	0.16	na	1.49	1.5 (1.5)
		210	1.05	na	na	0.51	na	4.68	na	0.52	1.7 (2.0)
		240	0.29	na	0.09	0.17	0.94	0.12	na	0.64	0.38 (0.34)

Table Ap.VIII.15: Total fatty acids data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.34	0.19	9.22	0.72	0.37	7.31	5.07	6.01	3.7 (3.7)
		75	1.08	na	9.19	2.72	5.21	na	5.59	2.35	4.4 (2.9)
		135	0.91	1.71	7.77	na	na	na	3.01	5.36	3.8 (2.8)
		195	1.27	1.31	4.21	3.18	na	na	7.69	2.94	3.4 (2.4)
	Aqueous phase	15	0.21	0.11	0.15	0.12	0.02	0.06	0.10	0.16	0.116 (0.059)
		75	0.44	0.49	0.10	0.12	0.13	na	0.30	0.02	0.23 (0.18)
		135	0.43	0.51	0.22	0.48	na	na	0.35	na	0.40 (0.12)
		195	0.12	0.14	na	0.12	na	na	na	<LOQ	0.094 (0.061)
Upper Small Intestine	Total aspirate	30	18.25	19.86	na	17.32	18.15	na	32.80	23.99	21.7 (5.9)
		60	17.45	na	11.75	na	10.71	14.53	34.79	34.93	20.7 (11.2)
		90	17.95	na	11.83	28.66	12.42	17.78	18.28	na	17.8 (6.0)
		120	16.51	na	9.79	18.20	na	13.70	11.45	na	13.9 (3.5)
		150	14.53	11.70	19.41	23.15	18.17	6.99	21.66	na	16.5 (5.8)
		180	10.01	8.23	8.48	10.38	na	12.45	17.67	na	11.2 (3.5)
		210	7.39	6.45	3.87	2.00	na	7.37	10.16	na	6.2 (2.9)
		240	3.34	5.43	3.19	0.75	2.51	5.20	5.28	na	3.7 (1.7)
	Micellar phase	30	8.16	na	na	0.03	11.47	13.34	na	na	8.2 (5.9)
		60	6.02	0.91	na	0.42	5.13	0.69	na	na	2.6 (2.7)
		90	2.12	0.62	na	1.15	5.21	0.98	na	na	2.0 (1.9)
		120	6.09	0.65	0.02	1.17	3.98	0.77	3.39	na	2.3 (2.2)
		150	3.96	na	na	0.02	na	0.78	1.74	na	1.6 (1.7)
		180	2.54	0.58	na	0.88	0.25	na	2.54	na	1.4 (1.1)
		210	1.23	3.26	na	0.52	1.40	2.77	5.14	na	2.4 (1.7)
		240	1.54	1.01	na	2.22	1.40	na	2.90	na	1.82 (0.75)

Table Ap.VIII.16: 1-mono-oleyl-rac-glycerol data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.01	<LOQ	0.34	0.08	0.32	0.45	0.06	0.13	0.17 (0.17)
		75	<LOQ	0.16	0.88	0.30	0.15	0.96	1.10	0.36	0.49 (0.42)
		135	0.07	0.09	1.16	0.32	0.34	0.82	0.11	0.21	0.39 (0.40)
		195	0.19	0.05	na	0.14	0.37	0.46	na	0.12	0.22 (0.16)
	Aqueous phase	15	<LOQ	0.01	0.25	0.01	na	0.07	<LOQ	0.01	0.050 (0.093)
		75	0.01	0.09	na	0.06	<LOQ	0.03	0.03	<LOQ	0.031 (0.033)
		135	0.03	0.06	0.01	0.04	<LOQ	na	0.04	<LOQ	0.026 (0.023)
		195	na	0.03	na	0.02	0.02	na	<LOQ	<LOQ	0.016 (0.015)
Upper Small Intestine	Total aspirate	30	0.91	0.88	0.78	na	na	2.35	2.14	1.11	1.36 (0.70)
		60	0.53	0.83	0.94	0.52	0.31	0.79	na	2.41	0.91 (0.70)
		90	2.00	0.45	na	1.23	0.79	1.18	<LOQ	0.82	0.92 (0.64)
		120	0.55	na	na	0.33	na	1.24	0.52	0.49	0.63 (0.35)
		150	0.30	0.66	na	na	0.50	0.76	0.84	0.35	0.57 (0.22)
		180	0.61	0.80	0.67	0.39	na	0.30	1.13	0.81	0.67 (0.28)
		210	0.23	0.36	0.13	0.29	0.56	<LOQ	na	0.66	0.32 (0.23)
		240	0.23	0.10	0.26	0.36	0.47	0.34	0.52	0.50	0.35 (0.15)
	Micellar phase	30	0.74	na	0.18	1.20	0.46	1.46	na	na	0.81 (0.52)
		60	4.43	na	0.38	0.48	0.25	0.47	na	0.12	1.0 (1.7)
		90	1.86	na	0.13	0.18	na	0.11	na	0.10	0.48 (0.77)
		120	0.52	0.31	na	<LOQ	na	0.11	0.47	0.27	0.28 (0.20)
		150	0.44	na	na	0.13	na	<LOQ	na	0.13	0.18 (0.19)
		180	0.68	0.58	0.03	<LOQ	0.12	<LOQ	na	0.16	0.22 (0.29)
		210	0.23	na	na	0.15	na	0.76	na	0.06	0.30 (0.32)
		240	0.04	na	0.03	0.02	0.23	<LOQ	na	0.08	0.066 (0.083)

Table Ap.VIII.17: 1-mono-oleyl-rac-glycerol data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.03	<LOQ	0.83	0.05	0.05	0.95	0.50	0.52	0.37 (0.39)
		75	0.08	na	0.80	0.13	0.44	na	0.55	0.25	0.37 (0.27)
		135	0.09	0.13	0.55	na	na	na	1.05	0.49	0.46 (0.39)
		195	0.22	0.08	0.45	0.15	na	na	0.63	0.33	0.31 (0.20)
	Aqueous phase	15	0.01	0.01	0.01	0.01	<LOQ	0.01	0.01	0.03	0.0111 (0.0074)
		75	0.03	0.05	<LOQ	0.01	0.01	na	0.05	<LOQ	0.023 (0.022)
		135	0.03	0.05	0.03	0.07	na	na	0.06	na	0.049 (0.019)
		195	0.02	0.01	na	0.03	na	na	na	<LOQ	0.017 (0.014)
Upper Small Intestine	Total aspirate	30	1.31	0.56	na	0.53	1.02	na	1.36	0.60	0.90 (0.39)
		60	1.29	na	0.59	na	0.82	2.14	1.06	1.10	1.17 (0.54)
		90	1.02	na	0.41	1.12	0.84	1.59	0.58	na	0.93 (0.42)
		120	1.66	na	0.55	0.50	na	1.42	0.71	na	0.97 (0.53)
		150	0.73	0.52	0.36	0.84	0.76	0.72	1.13	na	0.72 (0.24)
		180	0.30	0.49	0.16	0.33	na	0.37	0.52	na	0.36 (0.13)
		210	0.17	0.35	0.27	<LOQ	na	0.15	0.36	na	0.22 (0.14)
		240	0.11	0.36	<LOQ	<LOQ	0.22	0.31	0.29	na	0.18 (0.15)
	Micellar phase	30	1.17	na	na	<LOQ	1.02	0.88	na	na	0.77 (0.52)
		60	1.09	0.20	na	0.12	0.27	0.04	na	na	0.34 (0.43)
		90	0.21	0.21	na	0.20	0.37	0.14	na	na	0.22 (0.08)
		120	1.28	0.23	<LOQ	0.17	0.18	0.06	0.20	na	0.30 (0.44)
		150	0.51	na	na	<LOQ	na	0.10	0.11	na	0.18 (0.23)
		180	0.07	0.22	na	0.36	0.03	na	0.14	na	0.16 (0.13)
		210	0.01	0.64	na	0.15	0.05	0.11	0.31	na	0.21 (0.24)
		240	0.15	0.22	na	1.05	0.06	na	0.17	na	0.33 (0.40)

Table Ap.VIII.18: 1,2-dioleyl-rac-glycerol data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	<LOQ	0.06	4.60	0.71	2.77	4.61	0.16	2.45	1.9 (2.0)
		75	0.12	0.74	6.09	2.59	0.50	5.76	3.17	0.61	2.4 (2.4)
		135	0.31	0.66	3.33	1.62	1.54	4.09	3.24	0.14	1.9 (1.5)
		195	0.45	0.19	na	0.50	3.30	2.33	na	0.12	1.1 (1.3)
	Aqueous phase	15	0.01	<LOQ	<LOQ	<LOQ	na	<LOQ	0.01	<LOQ	0.0024 (0.0042)
		75	0.01	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.05	<LOQ	0.008 (0.018)
		135	0.06	<LOQ	na	<LOQ	<LOQ	na	<LOQ	<LOQ	0.011 (0.026)
		195	na	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ
Upper Small Intestine	Total aspirate	30	0.09	2.10	4.95	na	na	8.66	1.75	0.75	3.0 (3.2)
		60	0.04	0.51	0.93	0.68	0.18	0.55	na	2.12	0.72 (0.69)
		90	1.58	0.42	na	0.61	0.46	0.72	0.02	1.45	0.75 (0.57)
		120	0.48	na	na	0.79	na	0.69	0.44	1.28	0.74 (0.34)
		150	0.09	0.63	na	na	0.36	0.67	0.82	0.27	0.47 (0.28)
		180	3.01	<LOQ	0.27	0.69	na	0.43	1.08	0.54	0.9 (1.0)
		210	0.07	<LOQ	0.06	0.42	0.46	0.01	na	0.58	0.23 (0.25)
		240	0.11	<LOQ	0.06	0.29	0.22	0.20	0.41	0.43	0.22 (0.16)
	Micellar phase	30	0.02	na	<LOQ	0.03	<LOQ	<LOQ	na	na	0.011 (0.015)
		60	<LOQ	na	0.05	0.06	0.03	0.03	na	<LOQ	0.029 (0.025)
		90	<LOQ	na	0.03	0.05	na	<LOQ	na	<LOQ	0.017 (0.024)
		120	0.05	<LOQ	na	0.04	na	0.03	0.04	<LOQ	0.025 (0.020)
		150	<LOQ	na	na	0.07	na	<LOQ	na	<LOQ	0.018 (0.037)
		180	<LOQ	<LOQ	<LOQ	0.01	<LOQ	<LOQ	na	<LOQ	0.002 (0.005)
		210	<LOQ	na	na	0.01	na	<LOQ	na	<LOQ	0.0015 (0.0030)
		240	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ

Table Ap.VIII.19: 1,2-dioleyl-rac-glycerol data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.08	0.05	5.85	0.12	0.21	2.11	2.16	2.10	1.6 (2.0)
		75	0.35	na	4.10	0.57	3.10	na	3.07	0.69	2.0 (1.6)
		135	0.22	0.36	2.35	na	na	na	3.49	1.80	1.6 (1.4)
		195	0.33	0.27	1.48	0.54	na	na	2.57	1.01	1.03 (0.88)
	Aqueous phase	15	0.02	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.0027 (0.0076)
		75	0.10	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ	0.014 (0.036)
		135	0.07	<LOQ	<LOQ	<LOQ	na	na	<LOQ	na	0.014 (0.031)
		195	0.02	<LOQ	na	<LOQ	na	na	na	<LOQ	0.006 (0.012)
Upper Small Intestine	Total aspirate	30	0.28	0.47	na	0.86	0.40	na	0.52	0.41	0.49 (0.20)
		60	0.29	na	0.75	na	0.74	2.40	1.22	1.39	1.13 (0.73)
		90	0.56	na	0.98	1.64	0.73	1.97	0.80	na	1.11 (0.56)
		120	0.13	na	1.28	0.71	na	1.37	0.83	na	0.87 (0.50)
		150	0.33	0.75	0.39	1.31	0.15	0.77	0.96	na	0.67 (0.40)
		180	0.20	0.65	0.13	0.45	na	0.18	0.44	na	0.34 (0.20)
		210	0.14	<LOQ	<LOQ	0.10	na	0.09	0.16	na	0.082 (0.069)
		240	0.01	0.03	0.05	0.06	0.06	0.11	0.06	na	0.052 (0.031)
	Micellar phase	30	0.03	na	na	<LOQ	0.16	1.20	na	na	0.35 (0.57)
		60	0.03	0.15	na	<LOQ	0.08	<LOQ	na	na	0.051 (0.055)
		90	0.02	0.15	na	<LOQ	0.05	<LOQ	na	na	0.044 (0.064)
		120	<LOQ	<LOQ	<LOQ	<LOQ	0.03	<LOQ	<LOQ	na	0.004 (0.010)
		150	0.03	na	na	<LOQ	na	<LOQ	<LOQ	na	0.008 (0.016)
		180	<LOQ	0.15	na	<LOQ	<LOQ	na	<LOQ	na	0.031 (0.069)
		210	<LOQ	0.16	na	<LOQ	0.01	<LOQ	0.03	na	0.032 (0.063)
		240	<LOQ	<LOQ	na	<LOQ	0.01	na	<LOQ	na	0.0013 (0.0028)

Table Ap.VIII.20: Dipalmitin data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.06	0.15	2.06	0.48	0.62	2.54	0.26	0.84	0.88 (0.92)
		75	0.39	2.54	3.77	1.74	0.38	3.48	3.02	1.48	2.1 (1.3)
		135	1.02	2.16	3.20	1.38	1.00	3.10	2.41	0.46	1.8 (1.0)
		195	1.41	0.89	na	0.49	1.69	4.23	na	0.18	1.5 (1.5)
	Aqueous phase	15	0.01	0.01	0.17	0.03	na	0.04	0.01	<LOQ	0.041 (0.058)
		75	0.01	0.09	na	0.05	<LOQ	0.04	0.04	<LOQ	0.032 (0.033)
		135	0.03	0.08	0.01	0.02	<LOQ	na	0.04	<LOQ	0.026 (0.028)
		195	na	0.03	na	0.01	0.01	na	0.01	<LOQ	0.012 (0.012)
Upper Small Intestine	Total aspirate	30	0.12	1.60	4.04	na	na	7.51	1.17	1.41	2.6 (2.7)
		60	0.05	0.26	2.66	0.91	0.36	1.18	na	3.95	1.3 (1.4)
		90	0.65	0.23	na	1.24	1.25	1.91	0.03	3.02	1.2 (1.0)
		120	0.97	na	na	1.63	na	1.80	1.02	1.47	1.38 (0.37)
		150	0.12	1.42	na	na	0.95	2.09	1.91	0.46	1.16 (0.79)
		180	1.61	<LOQ	0.35	1.59	na	1.22	2.38	1.18	1.19 (0.80)
		210	0.07	<LOQ	0.10	1.08	1.65	0.02	na	1.32	0.61 (0.72)
		240	0.20	<LOQ	0.14	0.93	0.61	0.69	0.95	0.98	0.56 (0.40)
	Micellar phase	30	0.04	na	0.03	0.04	<LOQ	<LOQ	na	na	0.021 (0.020)
		60	<LOQ	na	0.17	0.08	0.06	0.10	na	<LOQ	0.068 (0.064)
		90	<LOQ	na	0.12	0.06	na	0.16	na	<LOQ	0.069 (0.072)
		120	0.08	<LOQ	na	0.05	na	0.05	0.09	0.04	0.051 (0.030)
		150	<LOQ	na	na	0.09	na	<LOQ	na	<LOQ	0.022 (0.045)
		180	<LOQ	0.04	0.03	0.02	<LOQ	<LOQ	na	0.04	0.020 (0.020)
		210	<LOQ	na	na	0.01	na	<LOQ	na	<LOQ	0.0026 (0.0052)
		240	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ

Table Ap.VIII.21: Dipalmitin data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.16	0.09	2.56	0.39	0.14	2.20	1.79	1.50	1.1 (1.0)
		75	0.98	na	2.20	1.91	1.74	na	2.10	0.61	1.59 (0.65)
		135	0.65	1.26	1.78	na	na	na	3.01	1.56	1.65 (0.87)
		195	0.85	2.86	1.02	1.57	na	na	2.02	0.85	1.53 (0.80)
	Aqueous phase	15	0.02	0.02	<LOQ	0.02	<LOQ	0.01	0.01	0.02	0.0106 (0.0085)
		75	0.05	0.07	<LOQ	0.01	<LOQ	na	0.02	<LOQ	0.021 (0.028)
		135	0.03	0.05	<LOQ	0.05	na	na	<LOQ	na	0.027 (0.022)
		195	0.01	0.01	na	0.01	na	na	na	<LOQ	0.0071 (0.0054)
Upper Small Intestine	Total aspirate	30	0.35	0.84	na	1.17	0.64	na	0.73	0.53	0.71 (0.28)
		60	0.38	na	1.19	na	1.23	3.48	1.86	2.25	1.7 (1.1)
		90	0.87	na	1.45	2.23	1.13	3.52	1.12	na	1.7 (1.0)
		120	0.12	na	1.88	0.99	na	2.61	1.50	na	1.42 (0.94)
		150	0.50	2.04	0.53	1.58	0.19	1.68	1.77	na	1.18 (0.75)
		180	0.23	1.30	0.18	0.65	na	0.30	1.14	na	0.63 (0.48)
		210	0.20	<LOQ	<LOQ	0.17	na	0.15	0.47	na	0.16 (0.17)
		240	0.01	0.05	0.05	0.09	0.12	0.21	0.09	na	0.087 (0.063)
	Micellar phase	30	0.03	na	na	<LOQ	0.17	0.26	na	na	0.11 (0.12)
		60	0.03	0.14	na	<LOQ	0.12	<LOQ	na	na	0.058 (0.069)
		90	0.03	0.14	na	0.03	0.06	<LOQ	na	na	0.052 (0.052)
		120	<LOQ	<LOQ	<LOQ	<LOQ	0.04	<LOQ	0.03	na	0.010 (0.017)
		150	0.03	na	na	<LOQ	na	<LOQ	<LOQ	na	0.006 (0.013)
		180	<LOQ	0.13	na	<LOQ	<LOQ	na	0.03	na	0.032 (0.054)
		210	<LOQ	0.13	na	<LOQ	0.01	<LOQ	0.04	na	0.030 (0.052)
		240	<LOQ	<LOQ	na	<LOQ	0.01	na	<LOQ	na	0.0017 (0.0039)

Table Ap.VIII.22: Total diglycerides data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.06	0.21	6.66	1.18	3.39	7.15	0.43	3.29	2.8 (2.9)
		75	0.51	3.28	9.86	4.33	0.89	9.25	6.19	2.09	4.5 (3.6)
		135	1.33	2.82	6.53	3.00	2.54	7.19	5.66	0.60	3.7 (2.4)
		195	1.86	1.08	na	0.99	4.99	6.56	na	0.30	2.6 (2.5)
	Aqueous phase	15	0.02	0.01	0.17	0.03	na	0.04	0.02	<LOQ	0.043 (0.057)
		75	0.02	0.09	na	0.05	<LOQ	0.04	0.09	<LOQ	0.041 (0.038)
		135	0.09	0.08	0.01	0.02	<LOQ	na	0.04	<LOQ	0.035 (0.038)
		195	na	0.03	na	0.01	0.01	na	0.01	<LOQ	0.012 (0.012)
Upper Small Intestine	Total aspirate	30	0.21	3.70	8.99	na	na	16.17	2.91	2.16	5.7 (5.9)
		60	0.09	0.77	3.59	1.59	0.54	1.73	na	6.07	2.1 (2.1)
		90	2.23	0.65	na	1.85	1.70	2.63	0.05	4.48	1.9 (1.4)
		120	1.44	na	na	2.42	na	2.50	1.47	2.75	2.12 (0.62)
		150	0.20	2.05	na	na	1.31	2.76	2.73	0.73	1.6 (1.1)
		180	4.62	<LOQ	0.62	2.28	na	1.64	3.45	1.72	2.0 (1.6)
		210	0.13	<LOQ	0.16	1.50	2.11	0.03	na	1.90	0.8 (1.0)
		240	0.30	<LOQ	0.20	1.23	0.84	0.89	1.36	1.42	0.78 (0.55)
	Micellar phase	30	0.06	na	0.03	0.07	<LOQ	<LOQ	na	na	0.032 (0.032)
		60	<LOQ	na	0.22	0.14	0.09	0.13	na	<LOQ	0.097 (0.085)
		90	<LOQ	na	0.16	0.11	na	0.16	na	<LOQ	0.086 (0.081)
		120	0.12	<LOQ	na	0.09	na	0.08	0.12	0.04	0.076 (0.048)
		150	<LOQ	na	na	0.16	na	<LOQ	na	<LOQ	0.041 (0.081)
		180	<LOQ	0.04	0.03	0.04	<LOQ	<LOQ	na	0.04	0.022 (0.021)
		210	<LOQ	na	na	0.02	na	<LOQ	na	<LOQ	0.004 (0.008)
		240	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ

Table Ap.VIII.23: Total diglycerides data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.25	0.14	8.40	0.51	0.35	4.31	3.95	3.59	2.7 (2.9)
		75	1.32	na	6.30	2.48	4.84	na	5.17	1.30	3.6 (2.1)
		135	0.87	1.63	4.14	na	na	na	6.50	3.36	3.3 (2.2)
		195	1.18	3.13	2.50	2.11	na	na	4.59	1.87	2.6 (1.2)
	Aqueous phase	15	0.04	0.02	<LOQ	0.02	<LOQ	0.01	0.01	0.02	0.013 (0.014)
		75	0.14	0.07	<LOQ	0.01	<LOQ	na	0.02	<LOQ	0.034 (0.054)
		135	0.10	0.05	<LOQ	0.05	na	na	<LOQ	na	0.040 (0.039)
		195	0.03	0.01	na	0.01	na	na	na	<LOQ	0.013 (0.015)
Upper Small Intestine	Total aspirate	30	0.63	1.31	na	2.03	1.04	na	1.24	0.94	1.20 (0.47)
		60	0.67	na	1.94	na	1.97	5.88	3.08	3.64	2.9 (1.8)
		90	1.43	na	2.44	3.87	1.86	5.48	1.92	na	2.8 (1.6)
		120	0.25	na	3.17	1.70	na	3.98	2.33	na	2.29 (1.43)
		150	0.83	2.79	0.92	2.89	0.33	2.44	2.72	na	1.8 (1.1)
		180	0.43	1.94	0.31	1.10	na	0.48	1.57	na	0.97 (0.68)
		210	0.34	<LOQ	<LOQ	0.27	na	0.24	0.63	na	0.25 (0.23)
		240	0.01	0.08	0.10	0.15	0.18	0.31	0.15	na	0.14 (0.09)
	Micellar phase	30	0.06	<LOQ	na	<LOQ	0.32	1.46	na	na	0.37 (0.62)
		60	0.05	0.30	na	<LOQ	0.20	<LOQ	na	na	0.11 (0.13)
		90	0.05	0.29	na	0.03	0.11	<LOQ	na	na	0.10 (0.12)
		120	<LOQ	<LOQ	<LOQ	<LOQ	0.06	<LOQ	0.03	na	0.013 (0.025)
		150	0.06	<LOQ	na	<LOQ	na	<LOQ	<LOQ	na	0.012 (0.026)
		180	<LOQ	0.28	na	<LOQ	<LOQ	na	0.03	na	0.06 (0.12)
		210	<LOQ	0.29	na	<LOQ	0.02	<LOQ	0.06	na	0.06 (0.11)
		240	<LOQ	<LOQ	na	<LOQ	0.01	na	<LOQ	na	0.0030 (0.0067)

Table Ap.VIII.24: Glyceryl trioleate data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.13	0.16	0.61	0.36	1.00	0.81	0.07	0.71	0.48 (0.35)
		75	0.27	0.37	0.56	0.62	0.25	0.69	0.52	0.83	0.51 (0.21)
		135	0.41	0.42	0.56	0.60	0.52	0.64	0.61	0.78	0.57 (0.12)
		195	0.54	0.25	na	0.28	0.60	0.57	na	0.24	0.41 (0.17)
	Aqueous phase	15	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ
		75	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
		135	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ
		195	na	<LOQ	na	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ
Upper Small Intestine	Total aspirate	30	<LOQ	0.70	0.72	na	na	3.46	1.22	0.45	1.1 (1.2)
		60	<LOQ	0.11	0.84	0.38	0.11	0.45	na	0.38	0.32 (0.29)
		90	0.56	0.25	na	0.13	0.19	0.12	0.22	0.28	0.25 (0.15)
		120	<LOQ	na	na	0.40	na	0.27	0.33	1.43	0.49 (0.55)
		150	<LOQ	<LOQ	na	na	0.61	0.60	0.39	0.44	0.34 (0.28)
		180	0.35	<LOQ	0.72	0.37	na	0.40	0.32	0.19	0.33 (0.22)
		210	<LOQ	<LOQ	0.10	0.26	0.54	<LOQ	na	0.18	0.15 (0.20)
		240	<LOQ	<LOQ	<LOQ	0.30	0.13	0.24	0.36	0.19	0.15 (0.14)
	Micellar phase	30	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ
		60	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ
		90	<LOQ	na	<LOQ	<LOQ	na	<LOQ	na	<LOQ	<LOQ
		120	<LOQ	<LOQ	na	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ
		150	<LOQ	na	na	<LOQ	na	<LOQ	na	<LOQ	<LOQ
		180	<LOQ	<LOQ	<LOQ	0.10	<LOQ	<LOQ	na	<LOQ	0.014 (0.036)
		210	<LOQ	na	na	<LOQ	na	<LOQ	na	<LOQ	<LOQ
		240	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ

Table Ap.VIII.25: Glyceryl trioleate data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.20	0.16	2.56	0.37	0.19	0.62	0.78	0.82	0.71 (0.79)
		75	0.43	na	2.20	0.59	0.66	na	0.81	0.60	0.88 (0.66)
		135	0.46	0.36	1.78	na	na	na	0.61	0.70	0.78 (0.57)
		195	0.42	0.47	1.02	0.51	na	na	0.60	0.61	0.60 (0.21)
	Aqueous phase	15	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
		75	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ
		135	<LOQ	<LOQ	<LOQ	<LOQ	na	na	<LOQ	na	<LOQ
		195	<LOQ	<LOQ	na	<LOQ	na	na	na	<LOQ	<LOQ
Upper Small Intestine	Total aspirate	30	0.06	0.13	na	0.22	<LOQ	na	0.07	0.07	0.092 (0.077)
		60	0.09	na	1.19	na	0.19	0.83	0.49	0.61	0.57 (0.41)
		90	0.25	na	1.45	0.40	0.23	0.37	0.16	na	0.48 (0.49)
		120	0.03	na	1.88	0.54	na	0.87	0.79	na	0.82 (0.68)
		150	0.11	0.69	0.53	0.54	<LOQ	0.85	0.32	na	0.44 (0.31)
		180	0.05	0.14	0.18	0.18	na	<LOQ	0.17	na	0.121 (0.077)
		210	0.08	<LOQ	<LOQ	0.08	na	<LOQ	<LOQ	na	0.028 (0.043)
		240	<LOQ	<LOQ	0.05	<LOQ	0.03	<LOQ	0.03	na	0.016 (0.022)
	Micellar phase	30	<LOQ	na	na	<LOQ	<LOQ	<LOQ	na	na	<LOQ
		60	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	na	na	<LOQ
		90	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	na	na	<LOQ
		120	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ
		150	<LOQ	na	na	<LOQ	na	<LOQ	<LOQ	na	<LOQ
		180	<LOQ	<LOQ	na	<LOQ	<LOQ	na	<LOQ	na	<LOQ
		210	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ
		240	<LOQ	<LOQ	na	<LOQ	<LOQ	na	<LOQ	na	<LOQ

Table Ap.VIII.26: Glyceryl trilinoleate data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.30	0.38	1.45	0.28	12.09	4.19	0.06	6.19	3.1 (4.3)
		75	0.21	0.91	1.22	1.85	0.43	1.19	1.06	8.04	1.9 (2.5)
		135	0.84	0.76	1.24	1.97	0.41	0.96	0.92	3.92	1.4 (1.1)
		195	0.75	0.28	na	0.32	1.16	0.98	na	2.68	1.03 (0.88)
	Aqueous phase	15	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ
		75	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
		135	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ
		195	na	<LOQ	na	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ
Upper Small Intestine	Total aspirate	30	<LOQ	3.71	<LOQ	na	na	na	4.73	0.97	1.9 (2.2)
		60	<LOQ	0.93	2.74	1.95	0.29	2.77	na	0.54	1.3 (1.2)
		90	8.97	1.75	na	0.12	0.31	0.18	0.09	0.13	1.7 (3.3)
		120	0.16	na	na	0.11	na	0.11	0.76	16.87	3.6 (7.4)
		150	<LOQ	0.07	na	na	1.00	0.26	0.19	1.29	0.47 (0.54)
		180	9.82	<LOQ	3.16	0.87	na	0.13	0.21	0.15	2.0 (3.6)
		210	<LOQ	<LOQ	0.43	0.19	0.59	<LOQ	na	0.12	0.19 (0.24)
		240	0.08	<LOQ	0.19	0.32	0.06	0.12	0.24	0.13	0.14 (0.10)
	Micellar phase	30	<LOQ	na	0.10	<LOQ	<LOQ	<LOQ	na	<LOQ	0.016 (0.040)
		60	<LOQ	na	0.16	<LOQ	<LOQ	<LOQ	na	<LOQ	0.027 (0.065)
		90	<LOQ	na	0.05	<LOQ	na	<LOQ	na	<LOQ	0.010 (0.021)
		120	<LOQ	<LOQ	na	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ
		150	<LOQ	na	na	<LOQ	na	<LOQ	na	<LOQ	<LOQ
		180	<LOQ	<LOQ	<LOQ	0.03	<LOQ	<LOQ	na	<LOQ	0.004 (0.010)
		210	<LOQ	na	na	<LOQ	na	<LOQ	na	<LOQ	<LOQ
		240	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ

Table Ap.VIII.27: Glyceryl trilinoleate data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.61	0.45	6.35	0.64	0.37	2.22	0.51	2.29	1.7 (2.0)
		75	2.19	na	3.38	2.08	2.34	na	2.19	1.38	2.26 (0.64)
		135	1.45	2.38	4.02	na	na	na	5.83	2.88	3.3 (1.7)
		195	1.46	1.93	2.28	2.04	na	na	4.81	1.34	2.3 (1.3)
	Aqueous phase	15	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
		75	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ
		135	<LOQ	<LOQ	<LOQ	<LOQ	na	na	<LOQ	na	<LOQ
		195	<LOQ	<LOQ	na	<LOQ	na	na	na	<LOQ	<LOQ
Upper Small Intestine	Total aspirate	30	0.26	0.46	na	0.41	0.11		0.13	0.21	0.26 (0.14)
		60	0.40	na	0.59	na	0.37	1.91	<LOQ	1.47	0.79 (0.74)
		90	0.82	na	0.62	0.47	0.49	0.75	5.08	na	1.4 (1.8)
		120	0.17	na	1.04	1.00	na	2.42	1.39	na	1.20 (0.81)
		150	0.46	2.19	0.25	0.53	<LOQ	1.77	<LOQ	na	0.74 (0.88)
		180	0.27	0.37	0.19	0.35	na	0.13	0.30	na	0.27 (0.10)
		210	0.34	<LOQ	<LOQ	0.20	na	0.08	0.11	na	0.12 (0.13)
		240	<LOQ	<LOQ	0.10	<LOQ	<LOQ	0.12	<LOQ	na	0.030 (0.052)
	Micellar phase	30	<LOQ	na	na	<LOQ	<LOQ	<LOQ	na	na	<LOQ
		60	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	na	na	<LOQ
		90	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	na	na	<LOQ
		120	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ
		150	<LOQ	na	na	<LOQ	na	<LOQ	<LOQ	na	<LOQ
		180	<LOQ	<LOQ	na	<LOQ	<LOQ	na	<LOQ	na	<LOQ
		210	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ
		240	<LOQ	<LOQ	na	<LOQ	<LOQ	na	<LOQ	na	<LOQ

Table Ap.VIII.28: Total triglycerides data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.44	0.55	2.06	0.64	13.10	5.00	0.13	6.90	3.6 (4.6)
		75	0.48	1.28	1.78	2.47	0.67	1.88	1.58	8.87	2.4 (2.7)
		135	1.25	1.17	1.80	2.57	0.93	1.60	1.54	4.70	1.9 (1.2)
		195	1.28	0.54	na	0.60	1.76	1.55	na	2.92	1.44 (0.88)
	Aqueous phase	15	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ
		75	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
		135	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ
		195	na	<LOQ	na	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ
Upper Small Intestine	Total aspirate	30	<LOQ	4.41	0.72	na	na	3.46	5.96	1.42	2.7 (2.3)
		60	<LOQ	1.04	3.58	2.33	0.40	3.21	<LOQ	0.92	1.4 (1.4)
		90	9.53	2.00	na	0.25	0.50	0.30	0.30	0.41	1.9 (3.4)
		120	0.16	na	na	0.51	na	0.37	1.10	18.30	4.1 (8.0)
		150	<LOQ	0.07	na	<LOQ	1.61	0.86	0.58	1.73	0.69 (0.74)
		180	10.17	<LOQ	3.88	1.23	na	0.53	0.52	0.34	2.4 (3.7)
		210	<LOQ	<LOQ	0.53	0.45	1.13	<LOQ	<LOQ	0.30	0.30 (0.40)
		240	0.08	<LOQ	0.19	0.61	0.19	0.35	0.60	0.32	0.29 (0.23)
	Micellar phase	30	<LOQ	na	0.10	<LOQ	<LOQ	<LOQ	na	<LOQ	0.016 (0.040)
		60	<LOQ	na	0.16	<LOQ	<LOQ	<LOQ	na	<LOQ	0.027 (0.065)
		90	<LOQ	na	0.05	<LOQ	na	<LOQ	na	<LOQ	0.010 (0.021)
		120	<LOQ	<LOQ	na	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ
		150	<LOQ	na	na	<LOQ	na	<LOQ	na	<LOQ	<LOQ
		180	<LOQ	<LOQ	<LOQ	0.12	<LOQ	<LOQ	na	<LOQ	0.018 (0.046)
		210	<LOQ	na	na	<LOQ	na	<LOQ	na	<LOQ	<LOQ
		240	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ

Table Ap.VIII.29: Total triglycerides data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.81	0.60	8.91	1.01	0.56	2.84	1.29	3.11	2.4 (2.8)
		75	2.63	na	5.58	2.67	3.00	na	2.99	1.97	3.1 (1.3)
		135	1.92	2.75	5.81	na	na	na	6.44	3.58	4.1 (2.0)
		195	1.88	2.40	3.30	2.56	na	na	5.41	1.94	2.9 (1.3)
	Aqueous phase	15	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
		75	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ
		135	<LOQ	<LOQ	<LOQ	<LOQ	na	na	<LOQ	na	<LOQ
		195	<LOQ	<LOQ	na	<LOQ	na	na	na	<LOQ	<LOQ
Upper Small Intestine	Total aspirate	30	0.31	0.59	na	0.64	0.11	na	0.20	0.28	0.36 (0.21)
		60	0.49	na	1.78	na	0.56	2.74	0.49	2.09	1.4 (1.0)
		90	1.07	na	2.07	0.87	0.72	1.12	5.24	na	1.8 (1.7)
		120	0.20	na	2.93	1.54	na	3.30	2.17	na	2.0 (1.2)
		150	0.57	2.89	0.77	1.07	<LOQ	2.62	0.32	na	1.2 (1.1)
		180	0.32	0.51	0.37	0.54	na	0.13	0.47	na	0.39 (0.15)
		210	0.43	<LOQ	<LOQ	0.28	na	0.08	0.11	na	0.15 (0.17)
		240	<LOQ	<LOQ	0.15	<LOQ	0.03	0.12	0.03	na	0.047 (0.061)
	Micellar phase	30	<LOQ	na	na	<LOQ	<LOQ	<LOQ	na	na	<LOQ
		60	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	na	na	<LOQ
		90	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	na	na	<LOQ
		120	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ
		150	<LOQ	na	na	<LOQ	na	<LOQ	<LOQ	na	<LOQ
		180	<LOQ	<LOQ	na	<LOQ	<LOQ	na	<LOQ	na	<LOQ
		210	<LOQ	<LOQ	na	<LOQ	<LOQ	<LOQ	<LOQ	na	<LOQ
		240	<LOQ	<LOQ	na	<LOQ	<LOQ	na	<LOQ	na	<LOQ

Table Ap.VIII.30: Lyso-phosphatidylcholine data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.01	<LOQ	0.12	<LOQ	0.08	0.12	<LOQ	<LOQ	0.041 (0.056)
		75	<LOQ	0.06	0.19	0.09	<LOQ	0.16	0.24	<LOQ	0.092 (0.093)
		135	<LOQ	0.06	0.13	0.09	0.08	0.17	0.11	<LOQ	0.080 (0.060)
		195	0.05	0.06	na	0.05	0.08	0.09	na	0.06	0.067 (0.018)
	Aqueous phase	15	<LOQ	<LOQ	0.09	<LOQ	na	0.01	<LOQ	<LOQ	0.015 (0.034)
		75	0.01	<LOQ	na	0.01	<LOQ	<LOQ	0.02	<LOQ	0.0053 (0.0069)
		135	0.02	0.01	<LOQ	0.01	<LOQ	na	<LOQ	<LOQ	0.0056 (0.0074)
		195	na	0.03	na	0.01	<LOQ	na	<LOQ	<LOQ	0.007 (0.012)
Upper Small Intestine	Total aspirate	30	1.75	0.96	0.76	na	na	2.85	4.79	2.72	2.3 (1.5)
		60	4.51	1.57	0.92	1.86	1.73	3.02	na	3.81	2.5 (1.3)
		90	1.37	1.31	na	2.32	1.31	1.91	0.54	2.20	1.57 (0.62)
		120	3.70	na	na	1.55	na	2.50	3.80	2.06	2.7 (1.0)
		150	1.90	1.21	na	na	0.79	0.62	2.55	1.73	1.47 (0.73)
		180	0.78	0.98	2.28	0.83	na	0.30	3.33	1.51	1.4 (1.1)
		210	1.07	0.88	0.61	0.91	0.59	1.79	na	1.38	1.03 (0.43)
		240	0.15	0.29	0.56	0.32	1.22	0.37	2.58	0.97	0.81 (0.80)
	Micellar phase	30	1.05	na	0.35	1.81	4.21	3.39	na	na	2.2 (1.6)
		60	3.19	na	0.67	0.64	0.75	1.21	na	0.08	1.1 (1.1)
		90	2.63	na	0.12	0.31	na	0.30	na	0.08	0.7 (1.1)
		120	1.18	0.50	na	0.07	na	0.21	1.53	0.44	0.65 (0.58)
		150	1.41	na	na	0.28	na	<LOQ	na	0.36	0.51 (0.62)
		180	1.74	0.72	0.06	<LOQ	0.08	<LOQ	na	0.40	0.43 (0.64)
		210	0.57	na	na	0.11	na	1.22	na	0.03	0.48 (0.54)
		240	<LOQ	na	0.01	<LOQ	0.22	<LOQ	na	0.06	0.05 (0.09)

Table Ap.VIII.31: Lyso-phosphatidylcholine data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.01	0.01	0.13	<LOQ	<LOQ	0.20	0.08	0.09	0.065 (0.074)
		75	0.40	na	0.09	0.06	0.07	na	0.07	0.05	0.13 (0.14)
		135	0.36	0.63	0.08	na	na	na	0.10	0.08	0.25 (0.24)
		195	0.49	0.44	0.07	0.06	na	na	0.08	0.06	0.20 (0.21)
	Aqueous phase	15	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.02	<LOQ	0.01	0.0041 (0.0078)
		75	0.01	0.02	<LOQ	<LOQ	<LOQ	na	0.01	<LOQ	0.0062 (0.0090)
		135	0.02	0.03	<LOQ	0.02	na	na	0.01	na	0.017 (0.012)
		195	0.02	0.01	na	0.01	na	na	na	<LOQ	0.0116 (0.0087)
Upper Small Intestine	Total aspirate	30	2.87	1.91	na	1.05	2.78	na	5.28	3.71	2.9 (1.5)
		60	2.26	na	1.68	na	2.64	0.79	4.29	4.50	2.7 (1.5)
		90	2.58	na	0.28	2.19	2.70	3.38	1.79	na	2.2 (1.1)
		120	2.47	na	0.97	2.06	na	0.31	1.10	na	1.38 (0.87)
		150	2.68	0.59	2.63	0.73	2.58	0.29	1.62	na	1.6 (1.1)
		180	0.95	0.55	1.69	0.45	na	2.59	3.08	na	1.6 (1.1)
		210	0.80	1.06	1.96	0.37	na	1.66	2.53	na	1.40 (0.80)
		240	0.57	0.48	0.68	0.13	1.05	0.88	1.46	na	0.75 (0.43)
	Micellar phase	30	1.66	na	na	<LOQ	3.18	2.32	na	na	1.8 (1.3)
		60	1.20	0.24	na	0.03	1.61	0.34	na	na	0.68 (0.69)
		90	0.88	0.20	na	0.24	1.39	0.22	na	na	0.59 (0.53)
		120	1.40	0.18	<LOQ	0.37	0.96	0.04	1.01	na	0.57 (0.55)
		150	1.53	na	na	<LOQ	na	0.04	0.41	na	0.50 (0.71)
		180	0.08	0.18	na	0.14	<LOQ	na	0.85	na	0.25 (0.34)
		210	0.03	0.97	na	0.05	0.56	0.93	1.52	na	0.68 (0.58)
		240	0.55	0.30	na	0.54	0.85	na	0.75	na	0.60 (0.21)

Table Ap.VIII.32: Egg phosphatidylcholine data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.39	0.79	10.06	2.09	4.11	7.33	0.70	2.81	3.5 (3.5)
		75	1.54	6.23	11.99	5.91	1.20	9.03	8.97	4.88	6.2 (3.7)
		135	3.02	5.75	9.03	4.73	3.10	7.92	7.58	3.04	5.5 (2.4)
		195	4.62	3.31	na	1.99	5.14	5.24	na	0.98	3.5 (1.8)
	Aqueous phase	15	0.08	0.12	3.62	0.30	na	1.51	0.07	0.25	0.8 (1.3)
		75	<LOQ	1.93	na	1.61	0.02	0.49	0.56	0.05	0.67 (0.79)
		135	0.56	1.61	0.18	1.03	0.04	na	0.56	0.04	0.57 (0.58)
		195	na	0.57	na	0.28	0.50	na	0.02	<LOQ	0.27 (0.26)
Upper Small Intestine	Total aspirate	30	0.47	17.14	<LOQ	na	na	na	9.88	2.53	6.0 (7.4)
		60	0.34	4.76	5.12	3.86	1.03	2.64	na	6.70	3.5 (2.3)
		90	12.10	3.64	na	2.16	3.24	3.19	0.67	5.26	4.3 (3.7)
		120	4.10	na	na	2.64	na	4.02	1.66	na	3.1 (1.2)
		150	0.42	3.64	na	na	2.69	6.03	2.90	1.27	2.8 (2.0)
		180	18.76	0.31	1.79	3.49	na	3.58	2.85	2.38	4.7 (6.3)
		210	0.33	0.04	0.61	1.65	3.57	0.06	na	2.65	1.3 (1.4)
		240	0.59	0.10	0.46	3.63	2.53	1.31	1.44	1.60	1.5 (1.2)
	Micellar phase	30	0.17	na	0.19	0.16	0.18	0.31	na	na	0.203 (0.064)
		60	0.20	na	0.41	0.26	0.18	0.18	na	0.03	0.21 (0.12)
		90	0.28	na	0.33	0.21	na	0.12	na	0.03	0.19 (0.12)
		120	0.26	0.10	na	0.19	na	0.05	0.19	0.10	0.148 (0.077)
		150	0.15	na	na	0.26	na	<LOQ	na	<LOQ	0.10 (0.13)
		180	0.17	0.09	0.12	0.08	0.01	<LOQ	na	0.08	0.08 (0.06)
		210	0.10	na	na	0.02	na	0.11	na	<LOQ	0.057 (0.057)
		240	<LOQ	na	<LOQ	<LOQ	0.10	<LOQ	na	<LOQ	0.016 (0.039)

Table Ap.VIII.33: Egg phosphatidylcholine data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	1.01	0.59	7.45	1.42	0.62	6.35	4.81	4.71	3.4 (2.8)
		75	3.99	na	7.16	4.77	6.89	na	6.30	2.07	5.2 (2.0)
		135	2.92	4.90	5.33	na	na	na	9.27	5.53	5.6 (2.3)
		195	3.93	2.90	3.62	4.79	na	na	7.08	2.93	4.2 (1.6)
	Aqueous phase	15	0.21	0.14	0.27	0.23	0.03	0.10	0.43	0.34	0.22 (0.13)
		75	0.83	1.81	0.22	0.32	0.17	na	0.98	0.04	0.63 (0.63)
		135	0.59	1.21	0.47	1.71	na	na	1.29	na	1.05 (0.51)
		195	0.25	0.21	na	0.26	na	na	na	0.02	0.19 (0.11)
Upper Small Intestine	Total aspirate	30	1.95	2.56	na	4.75	2.09	na	2.48	2.17	2.7 (1.0)
		60	1.71	na	10.34	<LOQ	3.37	10.05	5.23	5.45	5.2 (3.9)
		90	3.46	na	5.95	na	2.73	8.71	3.47	na	4.9 (2.5)
		120	1.06	na	7.69	3.84	na	6.95	5.10	na	4.9 (2.6)
		150	2.38	4.89	2.95	8.25	0.88	4.90	5.81	na	4.3 (2.4)
		180	1.28	3.21	0.90	3.32	na	1.18	2.05	na	2.0 (1.1)
		210	0.98	0.32	<LOQ	0.61	na	0.67	0.98	na	0.59 (0.38)
		240	0.04	0.60	0.34	0.28	0.68	0.65	0.46	na	0.44 (0.23)
	Micellar phase	30	0.28	na	na	<LOQ	<LOQ	0.85	na	na	0.28 (0.40)
		60	0.22	0.05	na	0.09	<LOQ	0.02	na	na	0.076 (0.089)
		90	0.17	0.04	na	0.15	<LOQ	0.03	na	na	0.079 (0.078)
		120	0.16	<LOQ	<LOQ	0.12	0.16	0.46	0.18	na	0.16 (0.15)
		150	0.24	na	na	<LOQ	na	0.21	0.10	na	0.14 (0.11)
		180	0.08	<LOQ	na	0.11	0.04	na	0.16	na	0.075 (0.060)
		210	0.03	0.14	na	<LOQ	<LOQ	0.13	0.21	na	0.085 (0.088)
		240	0.12	0.02	na	0.10	0.11	na	0.12	na	0.095 (0.041)

Table Ap.VIII.34: Total phosphatidylcholine data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.39	0.79	10.18	2.09	4.19	7.45	0.70	2.81	3.6 (3.5)
		75	1.54	6.29	12.18	6.00	1.20	9.19	9.20	4.88	6.3 (3.8)
		135	3.02	5.81	9.16	4.82	3.18	8.09	7.70	3.04	5.6 (2.5)
		195	4.67	3.36	na	2.04	5.22	5.33	na	1.05	3.6 (1.8)
	Aqueous phase	15	0.08	0.12	3.72	0.30	na	1.52	0.07	0.26	0.9 (1.4)
		75	0.01	1.93	na	1.62	0.02	0.49	0.57	0.05	0.67 (0.80)
		135	0.57	1.62	0.18	1.04	0.04	na	0.56	0.04	0.58 (0.58)
		195	na	0.60	na	0.28	0.50	na	0.02	<LOQ	0.28 (0.27)
Upper Small Intestine	Total aspirate	30	2.22	18.10	0.76	na	na	2.85	14.67	5.25	7.3 (7.3)
		60	4.85	6.33	6.04	5.72	2.76	5.65	na	10.50	6.0 (2.3)
		90	13.47	4.96	na	4.48	4.55	5.10	1.21	7.46	5.9 (3.8)
		120	7.80	na	na	4.18	na	6.52	5.47	2.06	5.2 (2.2)
		150	2.32	4.85	na	na	3.47	6.65	5.45	3.00	4.3 (1.6)
		180	19.55	1.30	4.07	4.31	na	3.88	6.18	3.89	6.2 (6.1)
		210	1.40	0.92	1.23	2.56	4.16	1.85	na	4.03	2.3 (1.3)
		240	0.74	0.39	1.03	3.94	3.75	1.67	4.02	2.58	2.3 (1.5)
	Micellar phase	30	1.23	na	0.54	1.97	4.39	3.71	na	<LOQ	2.0 (1.8)
		60	3.39	na	1.08	0.89	0.93	1.39	na	0.11	1.3 (1.1)
		90	2.91	na	0.46	0.52	na	0.42	na	0.11	0.9 (1.1)
		120	1.44	0.60	na	0.26	na	0.26	1.71	0.54	0.80 (0.62)
		150	1.56	na	na	0.53	na	<LOQ	na	0.36	0.61 (0.67)
		180	1.91	0.81	0.18	0.08	0.10	na	na	0.49	0.59 (0.70)
		210	0.67	na	na	0.13	na	1.33	na	0.03	0.54 (0.60)
		240	<LOQ	na	0.01	<LOQ	0.32	na	na	0.06	0.08 (0.14)

Table Ap.VIII.35: Total phosphatidylcholine data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	1.02	0.60	7.59	1.42	0.62	6.55	4.89	4.80	3.4 (2.8)
		75	4.40	na	7.26	4.83	6.96	na	6.37	2.12	5.3 (1.9)
		135	3.28	5.52	5.41	na	na	na	9.37	5.61	5.8 (2.2)
		195	4.42	3.34	3.69	4.86	na	na	7.17	2.98	4.4 (1.5)
	Aqueous phase	15	0.21	0.14	0.27	0.23	0.03	0.12	0.43	0.36	0.23 (0.13)
		75	0.85	1.83	0.22	0.32	0.17	na	0.99	0.04	0.63 (0.64)
		135	0.61	1.24	0.47	1.73	na	na	1.30	na	1.07 (0.52)
		195	0.28	0.22	na	0.27	na	na	na	0.02	0.20 (0.12)
Upper Small Intestine	Total aspirate	30	4.81	4.47	na	5.80	4.86	na	7.76	5.88	5.6 (1.2)
		60	3.97	na	12.02	na	6.02	10.84	9.52	9.95	8.7 (3.1)
		90	6.05	na	6.23	7.98	5.44	12.10	5.26	na	7.2 (2.6)
		120	3.53	na	8.66	5.90	na	7.26	6.20	na	6.3 (1.9)
		150	5.06	5.48	5.58	8.98	3.46	5.18	7.44	na	5.9 (1.8)
		180	2.23	3.76	2.59	3.78	na	3.77	5.13	na	3.5 (1.0)
		210	1.78	1.38	1.96	0.98	na	2.33	3.50	na	1.99 (0.88)
		240	0.62	1.08	1.02	0.41	1.73	1.54	1.92	na	1.19 (0.57)
	Micellar phase	30	1.94	na	na	<LOQ	3.18	3.17	na	na	2.1 (1.5)
		60	1.42	0.29	na	0.11	1.61	0.35	na	na	0.76 (0.70)
		90	1.06	0.24	na	0.39	1.39	0.25	na	na	0.67 (0.53)
		120	1.56	0.18	<LOQ	0.50	1.12	0.50	1.19	na	0.72 (0.58)
		150	1.77	na	na	<LOQ	na	0.25	0.52	na	0.63 (0.79)
		180	0.16	0.18	na	0.25	0.04	<LOQ	1.01	na	0.27 (0.37)
		210	0.06	1.11	na	0.05	0.56	1.06	1.73	na	0.76 (0.66)
		240	0.67	0.32	na	0.63	0.97	<LOQ	0.87	na	0.58 (0.36)

Table Ap.VIII.36: Cholesterol data (mM) after administration of drug solutions (Phase I)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.06	0.20	3.32	0.83	1.12	3.86	0.25	0.70	1.3 (1.5)
		75	0.38	1.13	4.97	2.49	0.39	3.22	4.19	1.86	2.3 (1.7)
		135	0.71	1.13	4.07	2.04	0.85	3.97	3.58	1.15	2.2 (1.5)
		195	<LOQ	0.71	na	0.85	2.95	2.76	na	0.47	1.3 (1.2)
	Aqueous phase	15	0.02	0.02	0.24	0.10	na	0.18	0.02	0.04	0.087 (0.089)
		75	0.29	0.10	na	0.32	<LOQ	0.09	0.10	0.01	0.13 (0.13)
		135	0.13	0.09	0.02	0.17	0.01	na	0.13	0.01	0.080 (0.070)
		195	na	0.14	na	0.05	0.06	na	0.01	<LOQ	0.055 (0.057)
Upper Small Intestine	Total aspirate	30	0.59	5.23	6.73	na	na	10.89	3.34	2.33	4.9 (3.7)
		60	1.51	1.02	3.60	2.24	1.42	2.15	na	4.83	2.4 (1.4)
		90	1.18	0.59	na	1.59	1.91	2.25	0.54	3.34	1.6 (1.0)
		120	1.72	na	na	1.14	na	2.69	2.01	2.41	1.99 (0.60)
		150	0.70	0.89	na	na	1.74	3.37	2.37	1.04	1.7 (1.0)
		180	0.89	0.48	1.27	1.28	na	2.18	2.93	1.63	1.52 (0.82)
		210	0.40	0.43	0.43	0.77	1.97	0.58	na	1.65	0.89 (0.65)
		240	0.19	0.22	0.48	0.88	1.19	1.12	1.40	1.33	0.85 (0.49)
	Micellar phase	30	0.35	na	0.15	0.95	2.48	1.13	na	na	1.01 (0.92)
		60	1.65	na	0.43	0.33	0.46	0.28	na	0.04	0.53 (0.57)
		90	1.03	na	0.22	0.18	na	0.09	na	0.04	0.31 (0.41)
		120	0.32	0.10	na	0.06	na	0.04	0.36	0.11	0.16 (0.14)
		150	0.35	na	na	0.19	na	<LOQ	na	0.07	0.16 (0.15)
		180	0.43	0.32	0.04	0.02	0.04	<LOQ	na	0.12	0.14 (0.17)
		210	0.12	na	na	0.02	na	0.39	na	0.03	0.14 (0.17)
		240	0.03	na	<LOQ	<LOQ	0.07	<LOQ	na	0.03	0.021 (0.027)

Table Ap.VIII.37: Cholesterol data (mM) after administration of drug suspensions (Phase II)

GI Location	Sample Phase	Time (min)	1	2	3	5	6	8	9	10	MEAN (SD)
Antrum	Total aspirate	15	0.23	0.14	3.96	0.21	0.24	2.43	2.31	2.28	1.5 (1.5)
		75	0.83	na	1.76	0.99	2.63	na	2.75	1.01	1.66 (0.86)
		135	0.55	0.88	2.30	na	na	na	3.95	2.32	2.0 (1.4)
		195	0.82	0.56	1.57	0.76	na	na	2.99	1.35	1.34 (0.89)
	Aqueous phase	15	0.08	0.03	0.05	0.06	<LOQ	0.03	0.08	0.07	0.049 (0.028)
		75	0.27	0.39	0.04	0.07	0.03	na	0.13	0.01	0.13 (0.14)
		135	0.18	0.24	0.06	0.30	na	na	0.16	na	0.187 (0.093)
		195	0.07	0.05	na	0.05	na	na	na	0.01	0.045 (0.026)
Upper Small Intestine	Total aspirate	30	1.21	1.59	na	1.35	2.48	na	2.54	1.76	1.82 (0.57)
		60	1.14	na	2.96	na	2.27	5.41	3.39	3.56	3.1 (1.4)
		90	1.12	na	3.42	4.51	2.22	2.18	2.63	na	2.7 (1.2)
		120	0.89	na	0.69	1.06	na	4.51	2.48	na	1.9 (1.6)
		150	1.04	2.52	1.16	1.18	1.22	2.32	2.81	na	1.75 (0.76)
		180	0.37	1.89	0.57	0.62	na	1.08	1.78	na	1.05 (0.65)
		210	0.33	0.38	0.90	0.18	na	0.56	1.06	na	0.57 (0.34)
		240	0.33	0.35	0.41	0.13	0.72	0.45	0.64	na	0.43 (0.20)
	Micellar phase	30	0.61	na	na	<LOQ	1.61	1.21	na	na	0.86 (0.70)
		60	0.41	0.18	na	<LOQ	0.63	0.08	na	na	0.26 (0.26)
		90	0.17	0.18	na	0.08	0.40	0.02	na	na	0.17 (0.14)
		120	0.48	0.17	<LOQ	0.07	0.23	0.06	0.21	na	0.17 (0.16)
		150	0.31	na	na	<LOQ	na	0.03	0.10	na	0.11 (0.14)
		180	0.03	0.17	na	0.05	<LOQ	na	0.18	na	0.085 (0.084)
		210	0.01	0.35	na	<LOQ	0.16	0.23	0.45	na	0.20 (0.18)
		240	0.16	0.19	na	0.05	0.36	na	0.21	na	0.194 (0.111)

APPENDIX IX Data from TIM-1 experiments

Table Ap.IX.1. Paracetamol TIM-1 data (µg/mL) after administration of aqueous paracetamol solution (Phase I)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1		Lab # 2	
			1	2	1	2
Antrum	Total sample	15	552.20	454.20	524.24	464.92
		75	415.50	328.90	399.36	376.09
		135	165.40	194.30	195.79	141.50
		180	58.40	102.00	80.03	122.17
Duodenum	Total sample	30	125.00	134.70	94.10	153.98
		60	306.10	225.70	337.51	318.93
		90	304.80	198.70	310.39	292.62
		120	237.00	224.40	249.06	226.41
		150	135.30	182.20	167.91	120.79
		180	58.40	94.00	82.33	52.30
		210	32.80	28.30	21.09	23.67
		240	11.30	15.00	5.36	6.81
	Micellar phase	30	108.10	na	na	na
		60	283.50	na	na	na
		90	294.70	na	na	na
		120	244.40	na	na	na
		150	119.10	na	na	na
		180	51.60	na	na	na
		210	27.80	na	na	na
		240	na	na	na	na
Jejunum	Total sample	30	27.50	na	12.09	14.41
		60	107.60	na	144.02	153.90
		90	127.90	na	178.31	313.87
		120	140.30	na	164.32	173.84
		150	108.30	na	129.60	104.51
		180	70.60	na	69.94	55.98
		210	28.60	na	25.50	24.69
		240	13.50	na	11.32	10.21
	Micellar phase	30	24.90	na	na	na
		60	105.90	na	na	na
		90	120.00	na	na	na
		120	130.80	na	na	na
		150	100.90	na	na	na
		180	62.30	na	na	na
		210	27.10	na	na	na
		240	13.40	na	na	na

Table Ap.IX.2. Paracetamol TIM-1 data (µg/mL) after administration of aqueous paracetamol suspension (Phase II)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1		Lab # 2	
			1	2	1	2
Antrum	Total sample	15	454.30	493.20	442.71	532.02
		75	399.50	351.50	351.15	379.37
		135	229.10	209.80	247.40	207.09
		180	98.60	76.50	148.62	22.81
Duodenum	Total sample	30	110.70	94.00	150.59	161.06
		60	314.40	251.80	257.44	311.15
		90	311.80	301.70	258.90	303.10
		120	251.80	256.70	230.63	253.55
		150	161.90	188.90	184.15	145.96
		180	66.60	85.10	125.61	56.49
		210	31.40	31.00	36.65	10.40
		240	10.90	22.00	13.40	3.70
	Micellar phase	30	91.10	na	na	na
		60	271.50	na	na	na
		90	282.50	na	na	na
		120	219.80	na	na	na
		150	144.40	na	na	na
		180	54.00	na	na	na
		210	24.00	na	na	na
		240	na	na	na	na
Jejunum	Total sample	30	6.20	11.20	22.98	35.32
		60	102.30	124.20	123.16	132.27
		90	114.90	156.10	144.87	171.22
		120	134.70	153.70	146.44	160.80
		150	110.20	96.50	140.99	106.53
		180	47.90	66.60	82.75	59.17
		210	29.40	27.70	34.48	23.84
		240	8.20	16.40	13.36	6.69
	Micellar phase	30	na	10.00	na	na
		60	na	114.50	na	na
		90	na	149.10	na	na
		120	na	144.70	na	na
		150	na	107.30	na	na
		180	na	60.70	na	na
		210	na	26.00	na	na
		240	na	15.10	na	na

Table Ap.IX.3. Danazol TIM-1 data (µg/mL) after administration of danazol sunflower oil solution (Phase I)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 2	
			1	2
Antrum	Total sample	15	3.25	39.31
		75	55.00	52.05
		135	199.87	127.37
		180	104.48	60.84
Duodenum	Total sample	30	2.50	3.82
		60	4.03	12.80
		90	22.29	8.15
		120	23.80	18.05
		150	23.51	10.87
		180	63.17	54.51
		210	51.14	49.50
		240	13.42	16.12
Jejunum	Total sample	30	2.50	0.57
		60	2.50	4.66
		90	7.06	7.51
		120	12.88	12.42
		150	13.95	15.67
		180	19.24	21.39
		210	40.42	31.49
		240	24.33	20.53

Table Ap.IX.4. Danazol TIM-1 data (µg/mL) after administration of aqueous danazol suspension (Phase II)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 2	
			1	2
Antrum	Total sample	15	65.79	67.31
		75	29.74	49.59
		135	30.41	33.64
		180	115.67	82.43
Duodenum	Total sample	30	20.41	15.69
		60	33.39	28.77
		90	34.39	31.86
		120	25.03	20.47
		150	18.20	11.87
		180	26.12	15.01
		210	26.95	15.07
		240	12.40	8.99
Jejunum	Total sample	30	3.43	3.68
		60	17.25	12.36
		90	18.18	18.37
		120	17.58	16.07
		150	12.36	6.34
		180	10.65	6.46
		210	10.53	9.64
		240	7.13	3.99

Table Ap.IX.5. Phenol red TIM-1 data (µg/mL)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 - Phase I		Lab # 1 - Phase II		Mean (SD)
			1	2	1	2	
Antrum	Total sample	15	55.57	65.59	75.06	71.84	67.0 (8.6)
		75	40.22	42.62	35.08	48.82	41.7 (5.7)
		135	18.69	30.07	20.88	22.35	23.0 (5.0)
		180	15.95	21.79	15.84	23.98	19.4 (4.1)
Duodenum	Total sample	30	32.44	18.84	25.65	38.01	28.7 (8.3)
		60	58.34	61.43	51.53	56.00	56.8 (4.2)
		90	49.95	47.78	59.85	35.89	48.4 (9.8)
		120	25.56	28.93	41.87	38.40	33.7 (7.7)
		150	12.54	15.67	25.32	26.99	20.1 (7.1)
		180	5.86	5.96	10.24	12.94	8.8 (3.5)
		210	5.42	8.94	5.22	5.37	6.2 (1.8)
		240	2.02	3.17	3.41	2.87	2.87 (0.61)

Table Ap.IX.6. pH data in TIM-1 gastric compartment

Time (min)	Lab # 1				Lab # 2				Median
	Phase I		Phase II		Phase I		Phase II		
	1	2	1	2	1	2	1	2	
1	6.3	6.7	6.5	6.5	6.5	6.7	6.2	6.2	6.5
5	6.3	6.4	6.4	6.4	6.4	6.7	6.2	6.3	6.4
10	6.1	6.1	5.9	5.7	6.0	6.6	6.1	6.0	6.1
15	5.6	5.7	5.8	5.8	5.7	6.0	6.0	5.6	5.8
20	5.6	5.5	5.5	5.5	5.4	5.3	5.6	5.4	5.5
25	5.1	5.4	5.2	5.1	5.4	5.3	5.3	5.4	5.3
30	4.9	5.0	5.0	4.8	4.9	5.0	5.0	5.0	5.0
35	4.6	4.8	4.7	4.6	4.6	4.6	4.6	4.7	4.6
40	4.4	4.5	4.4	4.4	4.5	4.4	4.6	4.5	4.5
45	4.2	4.2	4.2	4.2	4.3	4.2	4.2	4.3	4.2
50	4.0	4.0	4.1	4.1	4.3	4.1	3.9	4.1	4.1
55	3.8	3.8	3.8	3.7	4.1	4.0	3.9	3.8	3.8
60	3.6	3.5	3.6	3.6	3.7	3.4	3.6	3.6	3.6
65	3.3	3.3	3.3	3.3	3.5	3.4	3.3	3.2	3.3
70	3.1	3.1	3.0	3.0	3.2	3.3	3.1	3.1	3.1
75	2.9	3.0	2.8	2.9	3.1	3.0	2.9	2.9	2.9
80	2.8	2.8	2.9	2.7	2.9	2.9	2.8	2.7	2.8
85	2.5	2.6	2.6	2.6	2.6	2.7	2.8	2.7	2.6
90	2.5	2.4	2.5	2.5	2.5	2.5	2.6	2.4	2.5
95	2.4	2.4	2.4	2.4	2.3	2.3	2.5	2.2	2.4
100	2.2	2.3	2.3	2.3	2.3	2.3	2.4	2.3	2.3
105	2.1	2.4	2.1	2.3	2.2	2.3	2.5	2.2	2.3
110	2.0	2.2	2.2	2.2	2.2	2.2	2.3	2.1	2.2
115	1.8	2.0	2.0	2.0	2.0	2.1	2.1	2.0	2.0
120	1.9	1.8	1.8	1.7	1.9	1.9	2.1	1.9	1.9
125	1.8	1.9	1.8	1.9	1.8	1.8	2.1	1.9	1.9
130	1.8	1.9	1.8	1.9	1.8	1.8	2.2	2.0	1.9
135	2.0	1.9	1.8	1.8	1.9	1.9	2.2	1.8	1.9
140	1.5	1.9	1.9	1.8	2.0	1.9	2.0	1.8	1.9
145	1.7	1.9	2.0	1.8	1.8	1.9	2.1	1.7	1.9
150	1.5	1.8	1.7	1.6	1.9	1.8	2.1	1.8	1.8
155	1.8	1.8	1.8	1.4	1.8	1.8	2.1	1.8	1.8
160	1.7	1.8	1.8	1.5	1.8	1.7	2.1	1.7	1.8
165	2.4	1.7	1.7	1.8	1.9	1.6	2.1	1.9	1.9
170	2.1	1.8	1.7	1.8	2.0	1.7	2.1	1.9	1.9
175	1.8	1.8	2.0	1.9	2.0	1.8	2.1	1.9	1.9
180	1.6	1.9	1.5	1.8	2.1	1.8	2.1	1.9	1.9

Table Ap.IX.7. pH data in TIM-1 duodenal compartment

Time (min)	Lab # 1				Lab # 2				Median
	Phase I		Phase II		Phase I		Phase II		
	1	2	1	2	1	2	1	2	
1	7.3	6.8	7.1	7.2	6.8	6.9	7.1	6.9	7.0
5	7.4	6.7	7.3	7.4	6.8	7.0	7.3	6.8	7.2
10	7.1	6.6	7.1	7.2	6.4	6.7	7.0	6.6	6.9
15	6.9	6.6	7.0	7.1	6.2	6.4	6.8	6.4	6.7
20	6.7	6.5	6.9	7.0	6.1	6.3	6.7	6.3	6.6
25	6.6	6.5	6.8	6.9	6.0	6.2	6.6	6.3	6.6
30	6.4	6.4	6.6	6.6	5.9	6.0	6.5	6.2	6.4
35	6.2	6.3	6.3	6.4	5.8	5.9	6.3	6.1	6.3
40	6.0	6.1	6.1	6.1	5.9	5.8	6.1	5.9	6.1
45	5.8	5.9	5.8	5.9	5.8	5.8	5.9	5.7	5.8
50	5.7	5.7	5.8	5.7	5.8	5.9	5.7	5.8	5.8
55	5.7	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8
60	5.8	5.8	5.8	5.8	5.8	5.9	5.8	5.8	5.8
65	5.6	5.7	5.6	5.8	5.7	5.7	5.7	5.8	5.7
70	5.7	5.7	5.8	5.6	5.7	5.7	5.8	5.6	5.7
75	5.5	5.8	5.7	5.7	5.6	5.7	5.7	5.7	5.7
80	5.7	5.7	5.7	5.7	5.8	5.8	5.8	5.7	5.7
85	5.7	5.6	5.7	5.6	5.5	5.7	5.7	5.7	5.7
90	5.7	5.8	5.7	5.5	5.8	5.8	5.7	5.7	5.7
95	5.7	5.7	5.5	5.6	5.7	5.7	5.7	5.6	5.7
100	5.6	5.7	5.6	5.7	5.6	5.7	5.8	5.7	5.7
105	5.7	5.7	5.7	5.8	5.7	5.7	5.7	5.7	5.7
110	5.6	5.7	5.7	5.7	5.8	5.7	5.8	5.6	5.7
115	5.8	5.7	5.7	5.7	5.7	5.7	5.7	5.8	5.7
120	5.6	5.7	5.7	5.6	5.7	5.9	5.8	5.7	5.7
125	5.8	5.8	5.8	5.8	5.7	5.8	5.7	5.8	5.8
130	5.7	5.7	5.7	5.7	5.7	5.8	5.7	5.7	5.7
135	5.8	5.8	5.7	5.6	5.8	5.8	5.8	5.7	5.8
140	5.8	5.8	5.9	5.8	5.6	5.9	5.8	5.8	5.8
145	5.9	5.7	5.9	5.7	6.0	5.7	5.9	5.8	5.9
150	5.9	5.8	5.7	5.6	5.8	5.9	5.9	5.8	5.8
155	6.0	5.8	5.8	5.8	5.8	5.8	5.7	5.8	5.8
160	5.8	6.0	5.9	5.7	5.9	6.1	5.9	5.8	5.9
165	5.9	5.9	6.0	5.9	5.8	6.1	5.9	5.9	5.9
170	5.8	5.8	5.9	5.9	6.0	6.0	5.9	5.8	5.9
175	5.9	6.0	5.9	5.8	5.8	6.0	5.8	6.0	5.9
180	5.9	6.0	5.8	5.9	5.9	5.9	5.8	6.1	5.9
185	6.0	5.9	6.3	6.1	5.9	6.0	6.2	6.0	6.0
190	6.1	6.0	6.3	6.1	5.8	6.0	6.0	6.1	6.1
195	6.2	6.0	6.3	6.1	6.0	6.0	6.1	6.1	6.1
200	6.2	6.0	6.3	6.2	6.0	6.1	6.2	6.1	6.2
205	6.2	6.1	6.2	6.2	6.0	6.0	6.2	6.0	6.2
210	6.3	6.1	6.2	6.2	5.9	6.0	6.2	6.0	6.2
215	6.3	6.2	6.2	6.2	5.9	6.0	6.2	6.0	6.2
220	6.3	6.2	6.3	6.2	5.9	6.0	6.2	6.0	6.2
225	6.3	6.2	6.2	6.2	5.9	5.9	6.2	6.1	6.2
230	6.3	6.2	6.3	6.2	5.9	5.9	6.2	6.1	6.2
235	6.3	6.3	6.3	6.3	5.9	5.9	6.2	6.1	6.3
240	6.3	6.3	6.3	6.3	5.9	6.0	6.2	6.1	6.3

Table Ap.IX.8. pH data in TIM-1 jejunal compartment

Time (min)	Lab # 1				Lab # 2				Median
	Phase I		Phase II		Phase I		Phase II		
	1	2	1	2	1	2	1	2	
1	na	7.4	7.6	7.2	6.8	6.8	7.1	6.8	7.1
5	na	7.1	7.5	7.4	7.0	7.2	7.4	7.2	7.2
10	na	7.0	7.4	7.3	6.9	7.0	7.3	7.1	7.1
15	na	6.9	7.2	7.2	6.6	6.9	7.2	6.9	6.9
20	na	6.8	7.2	7.1	6.5	6.8	7.0	6.8	6.8
25	na	6.7	7.1	7.1	6.4	6.6	6.9	6.7	6.7
30	na	6.7	7.0	7.0	6.3	6.6	6.8	6.6	6.7
35	na	6.6	7.0	6.8	6.3	6.4	6.6	6.5	6.6
40	na	6.5	6.8	6.7	6.3	6.3	6.5	6.4	6.5
45	na	6.3	6.5	6.5	6.3	6.3	6.3	6.3	6.3
50	na	6.3	6.3	6.3	6.3	6.3	6.3	6.4	6.3
55	na	6.4	6.3	6.3	6.3	6.3	6.3	6.3	6.3
60	na	6.3	6.5	6.4	6.3	6.3	6.4	6.3	6.3
65	na	6.3	6.4	6.3	6.3	6.3	6.3	6.3	6.3
70	na	6.4	6.4	6.3	6.3	6.3	6.4	6.4	6.4
75	na	6.4	6.3	6.4	6.3	6.3	6.3	6.3	6.3
80	na	6.4	6.4	6.3	6.3	6.3	6.3	6.3	6.3
85	na	6.3	6.3	6.3	6.3	6.3	6.4	6.3	6.3
90	na	6.3	6.3	6.3	6.2	6.3	6.3	6.3	6.3
95	na	6.3	6.3	6.3	6.3	6.3	6.3	6.3	6.3
100	na	6.3	6.4	6.3	6.3	6.3	6.3	6.4	6.3
105	na	6.3	6.3	6.4	6.3	6.3	6.3	6.3	6.3
110	na	6.3	6.4	6.4	6.3	6.4	6.3	6.3	6.3
115	na	6.4	6.4	6.4	6.3	6.3	6.3	6.4	6.4
120	na	6.3	6.3	6.3	6.3	6.4	6.3	6.3	6.3
125	na	6.4	6.5	6.3	6.3	6.3	6.4	6.4	6.4
130	na	6.4	6.3	6.3	6.3	6.3	6.3	6.3	6.3
135	na	6.4	6.4	6.3	6.3	6.4	6.4	6.4	6.4
140	na	6.3	6.4	6.3	6.3	6.4	6.4	6.3	6.3
145	na	6.4	6.4	6.3	6.3	6.3	6.5	6.4	6.4
150	na	6.4	6.4	6.4	6.4	6.4	6.3	6.4	6.4
155	na	6.4	6.4	6.4	6.4	6.3	6.4	6.4	6.4
160	na	6.4	6.3	6.3	6.4	6.4	6.4	6.4	6.4
165	na	6.3	6.4	6.3	6.3	6.4	6.4	6.3	6.3
170	na	6.4	6.4	6.4	6.4	6.3	6.3	6.4	6.4
175	na	6.4	6.3	6.4	6.3	6.3	6.4	6.4	6.4
180	na	6.4	6.4	6.4	6.4	6.4	6.4	6.4	6.4
185	na	6.4	6.4	6.4	6.3	6.3	6.3	6.4	6.4
190	na	6.4	6.4	6.3	6.2	6.3	6.4	6.3	6.3
195	na	6.3	6.4	6.5	6.2	6.3	6.5	6.3	6.3
200	na	6.4	6.4	6.4	6.2	6.3	6.3	6.3	6.3
205	na	6.4	6.4	6.4	6.3	6.3	6.3	6.4	6.4
210	na	6.3	6.4	6.4	6.3	6.4	6.4	6.3	6.4
215	na	6.5	6.4	6.4	6.4	6.4	6.4	6.4	6.4
220	na	6.4	6.4	6.4	6.3	6.3	6.3	6.3	6.3
225	na	6.4	6.4	6.4	6.4	6.3	6.4	6.4	6.4
230	na	6.4	6.4	6.4	6.4	6.3	6.4	6.4	6.4
235	na	6.4	6.4	6.4	6.4	6.4	6.3	6.4	6.4
240	na	6.4	6.4	6.4	6.4	6.4	6.4	6.4	6.4

Table Ap.IX.9. TIM-1 glycohyocholic acid data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Duodenum	Total sample	30	3.53	2.43	3.69	2.48
		60	3.17	2.02	2.11	2.02
		90	1.99	1.48	2.22	1.61
		120	2.12	1.32	2.25	1.40
		150	2.35	1.52	2.55	1.47
		180	3.48	1.73	3.37	1.95
		210	3.80	2.36	3.61	2.13
		240	3.68	2.76	3.99	2.40
	Micellar phase	30	3.67	na	3.73	v
		60	2.54	na	2.54	na
		90	1.80	na	2.03	na
		120	2.16	na	2.08	na
		150	2.66	na	3.29	na
		180	3.32	na	2.51	na
		210	3.93	na	3.37	na
		240	4.10	na	3.70	na
Jejunum	Total sample	30	na	2.49	na	2.43
		60	na	2.08	na	2.04
		90	na	1.64	na	1.42
		120	na	1.41	na	1.52
		150	na	1.69	na	1.53
		180	na	1.82	na	1.51
		210	na	1.25	na	1.62
		240	na	2.06	na	1.67
	Micellar phase	30	na	3.04	na	2.88
		60	na	2.30	na	2.26
		90	na	1.76	na	1.53
		120	na	1.62	na	1.54
		150	na	2.19	na	1.42
		180	na	1.86	na	1.60
		210	na	2.01	na	1.69
		240	na	1.99	na	1.81

Table Ap.IX.10. TIM-1 taurocholic acid data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Duodenum	Total sample	30	1.21	1.06	1.51	1.42
		60	2.48	1.17	1.21	1.27
		90	1.17	1.11	1.79	1.47
		120	1.24	0.96	1.47	1.05
		150	1.14	1.01	1.76	1.04
		180	1.59	0.99	2.05	1.23
		210	1.57	1.29	2.04	1.36
		240	1.83	1.66	2.17	1.53
	Micellar phase	30	1.47	na	1.68	na
		60	1.65	na	1.68	na
		90	1.56	na	1.63	na
		120	1.58	na	1.46	na
		150	1.60	na	1.83	na
		180	1.86	na	1.52	na
		210	1.83	na	1.90	na
		240	1.89	na	2.26	na
Jejunum	Total sample	30	na	1.13	na	1.48
		60	na	1.12	na	1.18
		90	na	1.01	na	0.90
		120	na	0.82	na	1.00
		150	na	0.92	na	1.13
		180	na	1.35	na	1.33
		210	na	1.49	na	1.56
		240	na	1.44	na	1.73
	Micellar phase	30	na	1.48	na	1.72
		60	na	1.25	na	1.43
		90	na	1.04	na	1.32
		120	na	1.04	na	1.27
		150	na	1.65	na	1.34
		180	na	1.28	na	1.59
		210	na	1.69	na	1.81
		240	na	1.89	na	1.98

Table Ap.IX.11. TIM-1 glycohyodeoxycholic acid data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Duodenum	Total sample	30	4.87	4.31	5.67	5.27
		60	7.79	4.63	4.50	5.04
		90	4.68	4.19	5.82	5.64
		120	4.99	3.55	5.25	3.81
		150	4.73	4.02	5.86	4.33
		180	5.99	3.70	6.52	4.99
		210	6.28	4.84	6.71	5.45
		240	6.53	5.87	7.21	5.75
	Micellar phase	30	5.74	na	5.59	na
		60	5.32	na	5.23	na
		90	4.72	na	4.88	na
		120	5.14	na	4.91	na
		150	5.53	na	6.60	na
		180	6.19	na	5.29	na
		210	6.38	na	6.69	na
		240	6.69	na	7.39	na
Jejunum	Total sample	30	na	5.29	na	5.33
		60	na	4.44	na	5.10
		90	na	4.08	na	3.90
		120	na	3.30	na	3.70
		150	na	4.25	na	4.12
		180	na	4.91	na	4.50
		210	na	3.73	na	5.34
		240	na	5.37	na	5.60
	Micellar phase	30	na	6.05	na	6.17
		60	na	4.88	na	5.61
		90	na	4.11	na	4.66
		120	na	4.13	na	4.44
		150	na	6.25	na	4.83
		180	na	4.78	na	5.93
		210	na	6.00	na	6.13
		240	na	6.41	na	6.75

Table Ap.IX.12. TIM-1 taurochenodeoxycholic acid data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Duodenum	Total sample	30	1.42	1.26	1.46	1.44
		60	1.18	1.09	0.63	0.92
		90	0.84	0.93	0.78	0.78
		120	0.86	0.86	0.84	0.65
		150	0.95	0.93	0.95	0.70
		180	1.29	1.00	1.21	0.93
		210	1.45	1.19	1.34	1.09
		240	1.40	1.31	1.42	1.02
	Micellar phase	30	1.43	na	1.50	na
		60	0.88	na	0.92	na
		90	0.67	na	0.73	na
		120	0.73	na	0.75	na
		150	0.99	na	1.15	na
		180	1.25	na	0.91	na
		210	1.48	na	1.30	na
		240	1.41	na	1.40	na
Jejunum	Total sample	30	na	1.38	na	1.31
		60	na	1.11	na	1.08
		90	na	0.93	na	0.63
		120	na	0.84	na	0.68
		150	na	0.94	na	0.61
		180	na	0.94	na	0.68
		210	na	na	na	na
		240	na	1.10	na	0.75
	Micellar phase	30	na	1.23	na	1.39
		60	na	1.00	na	1.08
		90	na	0.88	na	0.71
		120	na	0.75	na	0.71
		150	na	1.08	na	0.64
		180	na	0.96	na	0.74
		210	na	1.00	na	0.79
		240	na	1.02	na	0.81

Table Ap.IX.13. TIM-1 glycochenodeoxycholic acid data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Duodenum	Total sample	30	4.49	4.59	5.54	5.14
		60	6.74	4.47	4.22	4.75
		90	4.05	3.75	5.16	5.42
		120	4.31	3.57	4.82	3.82
		150	4.10	3.76	5.39	3.96
		180	5.37	3.68	6.26	4.62
		210	5.69	5.02	6.48	5.48
		240	6.08	5.94	7.17	5.32
	Micellar phase	30	5.47	na	5.75	na
		60	4.91	na	5.23	na
		90	4.05	na	4.73	na
		120	4.46	na	4.65	na
		150	4.77	na	5.86	na
		180	5.60	na	4.85	na
		210	5.94	na	6.56	na
		240	6.24	na	7.38	na
Jejunum	Total sample	30	na	5.05	na	5.64
		60	na	4.07	na	4.66
		90	na	3.68	na	3.27
		120	na	3.24	na	3.54
		150	na	4.09	na	3.57
		180	na	2.15	na	4.12
		210	na	5.12	na	4.68
		240	na	5.18	na	4.92
	Micellar phase	30	na	5.72	na	6.70
		60	na	4.51	na	5.37
		90	na	3.87	na	4.11
		120	na	3.88	na	4.03
		150	na	5.92	na	4.09
		180	na	4.31	na	5.08
		210	na	5.79	na	5.33
		240	na	5.94	na	6.08

Table Ap.IX.14. TIM-1 total bile acids data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Duodenum	Total sample	30	15.52	13.65	17.87	15.75
		60	21.37	13.37	12.65	14.01
		90	12.73	11.45	15.77	14.92
		120	13.52	10.26	14.63	10.72
		150	13.27	11.23	16.51	11.50
		180	17.71	11.10	19.41	13.72
		210	18.79	14.70	20.19	15.50
		240	19.52	17.55	21.96	16.02
	Micellar phase	30	17.79	na	18.25	na
		60	15.30	na	15.60	na
		90	12.80	na	14.00	na
		120	14.07	na	13.86	na
		150	15.56	na	18.72	na
		180	18.22	na	15.08	na
		210	19.55	na	19.82	na
		240	20.33	na	22.14	na
Jejunum	Total sample	30	na	15.34	na	16.18
		60	na	12.83	na	14.05
		90	na	11.35	na	10.12
		120	na	9.61	na	10.44
		150	na	11.89	na	10.95
		180	na	11.17	na	12.14
		210	na	11.58	na	13.87
		240	na	15.14	na	14.68
	Micellar phase	30	na	17.52	na	18.85
		60	na	13.95	na	15.75
		90	na	11.66	na	12.34
		120	na	11.42	na	11.99
		150	na	17.10	na	12.32
		180	na	13.19	na	14.95
		210	na	16.49	na	15.75
		240	na	17.24	na	17.45

Table Ap.IX.15. TIM-1 linoleic acid data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	0.31	1.72	0.91	0.23
		75	0.40	1.28	1.69	0.38
		135	0.07	0.67	<LOQ	0.23
		180	<LOQ	0.31	0.20	0.05
Duodenum	Total sample	30	1.31	na	1.17	na
		60	0.28	na	3.67	na
		90	0.77	na	3.48	na
		120	0.55	na	2.73	na
		150	0.33	na	1.51	na
		180	0.65	na	1.62	na
		210	0.83	na	1.42	na
		240	0.77	na	0.61	na
	Micellar phase	30	1.34	na	1.79	na
		60	0.69	na	2.78	na
		90	0.41	na	2.49	na
		120	0.34	na	1.80	na
		150	0.61	na	1.15	na
		180	0.64	na	1.16	na
		210	0.88	na	0.95	na
		240	0.88	na	0.51	na
Jejunum	Total sample	30	na	1.24	na	0.30
		60	na	3.00	na	0.98
		90	na	2.49	na	0.69
		120	na	1.44	na	0.52
		150	na	1.82	na	na
		180	na	1.47	na	0.42
		210	na	1.10	na	0.44
		240	na	0.70	na	0.30
	Micellar phase	30	na	1.13	na	0.96
		60	na	2.43	na	0.97
		90	na	1.64	na	0.51
		120	na	1.37	na	0.71
		150	na	1.06	na	0.37
		180	na	1.09	na	0.34
		210	na	0.65	na	0.25
		240	na	0.42	na	0.19

Table Ap.IX.16. TIM-1 oleic acid data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	2.00	1.33	0.90	1.26
		75	2.26	1.29	1.41	2.06
		135	0.85	0.79	0.88	1.00
		180	<LOQ	0.49	0.63	0.57
Duodenum	Total sample	30	3.39	na	2.46	na
		60	2.14	na	3.10	na
		90	3.20	na	2.32	na
		120	na	na	2.61	na
		150	1.69	na	1.49	na
		180	1.63	na	1.27	na
		210	1.58	na	0.48	na
		240	1.04	na	0.78	na
	Micellar phase	30	3.40	na	2.81	na
		60	2.18	na	2.76	na
		90	1.56	na	2.17	na
		120	1.54	na	1.82	na
		150	1.51	na	1.25	na
		180	1.58	na	0.86	na
		210	1.65	na	0.71	na
		240	1.07	na	0.63	na
Jejunum	Total sample	30	na	1.38	na	0.75
		60	na	2.65	na	3.56
		90	na	2.23	na	2.75
		120	na	1.73	na	2.93
		150	na	1.73	na	na
		180	na	1.69	na	2.14
		210	na	0.79	na	1.95
		240	na	0.68	na	1.37
	Micellar phase	30	na	1.38	na	0.94
		60	na	2.54	na	3.06
		90	na	2.00	na	2.59
		120	na	1.54	na	2.19
		150	na	1.33	na	1.71
		180	na	0.93	na	1.26
		210	na	0.83	na	1.01
		240	na	0.62	na	0.92

Table Ap.IX.17. TIM-1 stearic acid data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	0.62	0.72	0.50	0.84
		75	1.25	0.59	0.27	0.88
		135	0.30	0.36	0.35	0.41
		180	<LOQ	0.21	<LOQ	0.02
Duodenum	Total sample	30	0.90	na	0.18	na
		60	1.59	na	1.13	na
		90	1.54	na	1.10	na
		120	0.97	na	0.86	na
		150	0.80	na	0.63	na
		180	0.68	na	0.46	na
		210	0.50	na	0.23	na
		240	0.48	na	0.22	na
	Micellar phase	30	0.53	na	0.35	na
		60	0.54	na	0.52	na
		90	0.36	na	0.19	na
		120	0.37	na	0.37	na
		150	0.32	na	0.39	na
		180	0.45	na	0.34	na
		210	0.44	na	0.25	na
		240	0.23	na	0.26	na
Jejunum	Total sample	30	na	0.42	na	0.05
		60	na	0.98	na	0.94
		90	na	1.07	na	0.95
		120	na	1.12	na	1.19
		150	na	1.09	na	1.32
		180	na	1.08	na	1.10
		210	na	0.51	na	1.06
		240	na	0.66	na	0.90
	Micellar phase	30	na	0.20	na	0.29
		60	na	0.33	na	0.38
		90	na	0.25	na	0.47
		120	na	0.27	na	0.25
		150	na	0.17	na	0.22
		180	na	0.45	na	0.12
		210	na	0.09	na	0.39
		240	na	0.14	na	0.16

Table Ap.IX.18 TIM-1 total fatty acids data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	2.93	3.77	2.31	2.33
		75	3.91	3.16	3.37	3.32
		135	1.22	1.81	1.23	1.64
		180	<LOQ	1.01	0.83	0.65
Duodenum	Total sample	30	5.60	na	3.81	na
		60	4.00	na	7.90	na
		90	5.52	na	6.90	na
		120	1.52	na	6.20	na
		150	na	na	3.63	na
		180	2.96	na	3.35	na
		210	2.92	na	2.13	na
		240	2.28	na	1.61	na
	Micellar phase	30	5.28	na	4.95	na
		60	3.42	na	6.05	na
		90	2.33	na	4.85	na
		120	2.25	na	4.00	na
		150	2.43	na	2.79	na
		180	2.67	na	2.36	na
		210	2.97	na	1.92	na
		240	2.17	na	1.40	na
Jejunum	Total sample	30	na	3.05	na	1.10
		60	na	6.62	na	5.48
		90	na	5.79	na	4.39
		120	na	4.29	na	4.64
		150	na	4.64	na	na
		180	na	4.24	na	3.66
		210	na	2.40	na	3.45
		240	na	2.04	na	2.57
	Micellar phase	30	na	2.70	na	2.18
		60	na	5.30	na	4.41
		90	na	3.89	na	3.57
		120	na	3.19	na	3.14
		150	na	2.56	na	2.30
		180	na	2.46	na	1.72
		210	na	1.57	na	1.66
		240	na	1.18	na	1.26

Table Ap.IX.19. TIM-1 1-mono-oleyl-rac-glycerol data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	0.29	0.18	0.15	0.28
		75	0.26	0.15	0.17	0.26
		135	0.15	0.11	<LOQ	0.18
		180	<LOQ	<LOQ	<LOQ	<LOQ
Duodenum	Total sample	30	0.25	na	0.18	na
		60	0.18	na	<LOQ	na
		90	0.37	na	0.16	na
		120	0.30	na	<LOQ	na
		150	0.26	na	<LOQ	na
		180	0.19	na	<LOQ	na
		210	0.21	na	<LOQ	na
		240	0.17	na	<LOQ	na
	Micellar phase	30	0.36	na	0.28	na
		60	0.35	na	0.33	na
		90	0.16	na	<LOQ	na
		120	0.27	na	<LOQ	na
		150	0.26	na	<LOQ	na
		180	0.17	na	<LOQ	na
		210	0.23	na	<LOQ	na
		240	0.16	na	<LOQ	na
Jejunum	Total sample	30	na	0.18	na	0.13
		60	na	0.20	na	0.24
		90	na	0.21	na	0.23
		120	na	<LOQ	na	0.29
		150	na	<LOQ	na	na
		180	na	<LOQ	na	na
		210	na	<LOQ	na	na
		240	na	<LOQ	na	na
	Micellar phase	30	na	0.43	na	0.40
		60	na	0.50	na	0.57
		90	na	0.39	na	0.42
		120	na	0.31	na	0.37
		150	na	0.28	na	0.33
		180	na	0.21	na	0.27
		210	na	0.14	na	0.14
		240	na	<LOQ	na	0.18

Table Ap.IX.20. TIM-1 1.2-dioleyl-rac-glycerol data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	0.19	0.26	0.23	0.14
		75	0.33	0.24	0.32	0.30
		135	0.08	0.18	0.21	na
		180	<LOQ	0.18	<LOQ	0.02
Duodenum	Total sample	30	0.18	na	0.15	na
		60	0.46	na	0.16	na
		90	0.26	na	0.30	na
		120	0.16	na	0.13	na
		150	0.09	na	0.20	na
		180	0.03	na	0.15	na
		210	<LOQ	na	<LOQ	na
		240	<LOQ	na	<LOQ	na
	Micellar phase	30	0.09	na	0.18	na
		60	0.03	na	<LOQ	na
		90	<LOQ	na	<LOQ	na
		120	<LOQ	na	<LOQ	na
		150	<LOQ	na	<LOQ	na
		180	<LOQ	na	<LOQ	na
		210	<LOQ	na	<LOQ	na
		240	<LOQ	na	<LOQ	na
Jejunum	Total sample	30	na	0.14	na	<LOQ
		60	na	0.17	na	0.17
		90	na	0.19	na	0.16
		120	na	0.20	na	0.15
		150	na	0.19	na	0.21
		180	na	0.19	na	0.18
		210	na	0.12	na	0.12
		240	na	0.12	na	0.12
	Micellar phase	30	na	<LOQ	na	<LOQ
		60	na	0.14	na	0.02
		90	na	0.14	na	0.05
		120	na	0.12	na	0.01
		150	na	0.12	na	<LOQ
		180	na	0.11	na	<LOQ
		210	na	<LOQ	na	<LOQ
		240	na	<LOQ	na	<LOQ

Table Ap.IX.21. TIM-1 dipalmitin data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	0.92	0.45	0.40	0.47
		75	0.84	0.52	0.67	0.80
		135	0.22	0.33	0.35	na
		180	<LOQ	0.26	0.34	0.11
Duodenum	Total sample	30	0.35	na	0.15	na
		60	0.72	na	0.17	na
		90	0.63	na	0.52	na
		120	0.49	na	0.14	na
		150	0.36	na	na	na
		180	0.21	na	0.19	na
		210	0.14	na	<LOQ	na
		240	<LOQ	na	<LOQ	na
	Micellar phase	30	0.25	na	0.21	na
		60	0.18	na	<LOQ	na
		90	0.14	na	<LOQ	na
		120	0.15	na	<LOQ	na
		150	0.15	na	<LOQ	na
		180	0.22	na	<LOQ	na
		210	0.09	na	<LOQ	na
		240	0.07	na	<LOQ	na
Jejunum	Total sample	30	na	0.10	na	0.09
		60	na	0.22	na	0.39
		90	na	0.20	na	0.32
		120	na	0.30	na	0.44
		150	na	0.26	na	0.60
		180	na	0.23	na	0.59
		210	na	0.47	na	0.33
		240	na	0.07	na	0.37
	Micellar phase	30	na	<LOQ	na	<LOQ
		60	na	0.18	na	0.20
		90	na	0.15	na	0.20
		120	na	0.11	na	0.12
		150	na	0.09	na	0.11
		180	na	<LOQ	na	<LOQ
		210	na	<LOQ	na	<LOQ
		240	na	<LOQ	na	<LOQ

Table Ap.IX.22. TIM-1 total diglycerides data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	1.11	0.71	0.63	0.61
		75	1.17	0.77	0.98	1.10
		135	0.30	0.51	0.55	na
		180	<LOQ	0.43	0.34	0.13
Duodenum	Total sample	30	0.54	na	0.30	na
		60	1.18	na	0.32	na
		90	0.89	na	0.82	na
		120	0.65	na	0.26	na
		150	0.45	na	0.20	na
		180	0.24	na	0.34	na
		210	0.14	na	<LOQ	na
		240	<LOQ	na	<LOQ	na
	Micellar phase	30	0.34	na	0.39	na
		60	0.21	na	<LOQ	na
		90	0.13	na	<LOQ	na
		120	0.15	na	<LOQ	na
		150	0.15	na	<LOQ	na
		180	0.22	na	<LOQ	na
		210	0.09	na	<LOQ	na
		240	0.07	na	<LOQ	na
Jejunum	Total sample	30	na	0.24	na	0.09
		60	na	0.39	na	0.56
		90	na	0.39	na	0.47
		120	na	0.50	na	0.59
		150	na	0.46	na	0.82
		180	na	0.42	na	0.77
		210	na	0.58	na	0.44
		240	na	0.19	na	0.49
	Micellar phase	30	na	<LOQ	na	<LOQ
		60	na	0.32	na	0.21
		90	na	0.28	na	0.25
		120	na	0.23	na	0.13
		150	na	0.21	na	0.11
		180	na	0.11	na	<LOQ
		210	na	<LOQ	na	<LOQ
		240	na	<LOQ	na	<LOQ

Table Ap.IX.23. TIM-1 glyceryl trioleate data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	<LOQ	0.22	0.19	<LOQ
		75	0.28	0.14	<LOQ	0.03
		135	<LOQ	<LOQ	0.11	<LOQ
		180	<LOQ	0.02	<LOQ	<LOQ
Duodenum	Total sample	30	<LOQ	na	<LOQ	na
		60	0.19	na	<LOQ	na
		90	0.12	na	0.04	na
		120	0.07	na	<LOQ	na
		150	0.09	na	<LOQ	na
		180	<LOQ	na	<LOQ	na
		210	<LOQ	na	<LOQ	na
		240	<LOQ	na	<LOQ	na
	Micellar phase	30	<LOQ	na	<LOQ	na
		60	<LOQ	na	<LOQ	na
		90	<LOQ	na	<LOQ	na
		120	<LOQ	na	<LOQ	na
		150	<LOQ	na	<LOQ	na
		180	<LOQ	na	<LOQ	na
		210	<LOQ	na	<LOQ	na
		240	<LOQ	na	<LOQ	na
Jejunum	Total sample	30	na	<LOQ	na	<LOQ
		60	na	<LOQ	na	<LOQ
		90	na	<LOQ	na	<LOQ
		120	na	0.07	na	0.13
		150	na	0.03	na	0.06
		180	na	<LOQ	na	<LOQ
		210	na	<LOQ	na	<LOQ
		240	na	<LOQ	na	<LOQ
	Micellar phase	30	na	<LOQ	na	<LOQ
		60	na	<LOQ	na	<LOQ
		90	na	<LOQ	na	<LOQ
		120	na	<LOQ	na	<LOQ
		150	na	<LOQ	na	<LOQ
		180	na	<LOQ	na	<LOQ
		210	na	<LOQ	na	<LOQ
		240	na	<LOQ	na	<LOQ

Table Ap.IX.24. TIM-1 glyceryl trilinoleate data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	0.25	0.23	0.20	0.31
		75	0.29	0.19	0.08	0.41
		135	0.06	0.06	0.15	0.18
		180	0.04	0.08	0.04	0.08
Duodenum	Total sample	30	0.06	na	0.13	na
		60	0.16	na	0.16	na
		90	0.12	na	0.33	na
		120	0.09	na	0.02	na
		150	0.05	na	0.10	na
		180	0.01	na	0.07	na
		210	<LOQ	na	0.03	na
		240	<LOQ	na	<LOQ	na
	Micellar phase	30	<LOQ	na	<LOQ	na
		60	<LOQ	na	<LOQ	na
		90	<LOQ	na	<LOQ	na
		120	<LOQ	na	<LOQ	na
		150	<LOQ	na	<LOQ	na
		180	<LOQ	na	<LOQ	na
		210	<LOQ	na	<LOQ	na
		240	<LOQ	na	<LOQ	na
Jejunum	Total sample	30	na	0.01	na	<LOQ
		60	na	0.04	na	0.07
		90	na	0.03	na	0.11
		120	na	0.10	na	0.11
		150	na	0.08	na	0.18
		180	na	0.01	na	0.04
		210	na	<LOQ	na	0.06
		240	na	<LOQ	na	0.02
	Micellar phase	30	na	<LOQ	na	<LOQ
		60	na	<LOQ	na	<LOQ
		90	na	<LOQ	na	<LOQ
		120	na	<LOQ	na	<LOQ
		150	na	<LOQ	na	<LOQ
		180	na	<LOQ	na	<LOQ
		210	na	<LOQ	na	<LOQ
		240	na	<LOQ	na	<LOQ

Table Ap.IX.25. TIM-1 total triglycerides data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	0.25	0.45	0.39	0.31
		75	0.57	0.34	0.08	0.45
		135	0.06	0.06	0.26	0.18
		180	0.04	0.10	0.04	0.08
Duodenum	Total sample	30	0.06	na	0.13	na
		60	0.35	na	0.16	na
		90	0.24	na	0.38	na
		120	0.17	na	0.02	na
		150	0.13	na	0.10	na
		180	0.01	na	0.07	na
		210	<LOQ	na	0.03	na
		240	<LOQ	na	<LOQ	na
	Micellar phase	30	<LOQ	na	<LOQ	na
		60	<LOQ	na	<LOQ	na
		90	<LOQ	na	<LOQ	na
		120	<LOQ	na	<LOQ	na
		150	<LOQ	na	<LOQ	na
		180	<LOQ	na	<LOQ	na
		210	<LOQ	na	<LOQ	na
		240	<LOQ	na	<LOQ	na
Jejunum	Total sample	30	na	0.01	na	<LOQ
		60	na	0.04	na	0.07
		90	na	0.03	na	0.11
		120	na	0.16	na	0.24
		150	na	0.11	na	0.24
		180	na	0.01	na	0.04
		210	na	<LOQ	na	0.06
		240	na	<LOQ	na	0.02
	Micellar phase	30	na	<LOQ	na	<LOQ
		60	na	<LOQ	na	<LOQ
		90	na	<LOQ	na	<LOQ
		120	na	<LOQ	na	<LOQ
		150	na	<LOQ	na	<LOQ
		180	na	<LOQ	na	<LOQ
		210	na	<LOQ	na	<LOQ
		240	na	<LOQ	na	<LOQ

Table Ap.IX.26. TIM-1 lyso-phosphatidylcholine data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	<LOQ	<LOQ	0.22	<LOQ
		75	<LOQ	<LOQ	0.18	<LOQ
		135	<LOQ	<LOQ	0.40	<LOQ
		180	<LOQ	<LOQ	<LOQ	0.00
Duodenum	Total sample	30	1.58	na	1.50	na
		60	0.86	na	0.69	na
		90	1.48	na	0.38	na
		120	0.49	na	0.36	na
		150	0.62	na	0.37	na
		180	0.81	na	0.38	na
		210	0.91	na	0.49	na
		240	1.00	na	0.56	na
	Micellar phase	30	2.61	na	2.66	na
		60	0.94	na	1.11	na
		90	0.64	na	0.56	na
		120	0.57	na	0.52	na
		150	0.83	na	0.53	na
		180	0.84	na	0.52	na
		210	1.24	na	0.79	na
		240	1.15	na	0.83	na
Jejunum	Total sample	30	na	0.70	na	1.09
		60	na	0.66	na	0.81
		90	na	0.43	na	0.54
		120	na	0.35	na	0.43
		150	na	0.31	na	na
		180	na	0.29	na	0.24
		210	na	0.28	na	0.24
		240	na	0.25	na	0.20
	Micellar phase	30	na	1.14	na	1.52
		60	na	1.03	na	1.23
		90	na	0.63	na	0.83
		120	na	0.52	na	0.57
		150	na	0.40	na	0.45
		180	na	0.36	na	0.35
		210	na	0.31	na	0.36
		240	na	0.30	na	0.31

Table Ap.IX.27. TIM-1 egg phosphatidylcholine data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	3.29	2.19	2.12	2.81
		75	2.54	1.72	2.21	2.51
		135	1.28	1.45	1.82	2.10
		180	1.02	1.54	1.47	0.54
Duodenum	Total sample	30	3.69	na	1.85	na
		60	4.70	na	2.03	na
		90	3.71	na	3.94	na
		120	2.57	na	1.23	na
		150	2.29	na	3.11	na
		180	2.58	na	3.33	na
		210	2.83	na	3.77	na
		240	2.51	na	2.71	na
	Micellar phase	30	3.47	na	2.89	na
		60	2.40	na	3.09	na
		90	1.64	na	1.04	na
		120	1.70	na	0.94	na
		150	1.79	na	0.95	na
		180	2.27	na	2.89	na
		210	2.46	na	2.41	na
		240	2.11	na	1.80	na
Jejunum	Total sample	30	na	2.83	na	1.34
		60	na	3.38	na	3.80
		90	na	2.67	na	3.14
		120	na	2.41	na	2.34
		150	na	2.25	na	2.77
		180	na	2.12	na	2.49
		210	na	2.09	na	2.19
		240	na	1.73	na	2.21
	Micellar phase	30	na	1.92	na	1.64
		60	na	2.78	na	2.86
		90	na	1.96	na	2.72
		120	na	1.68	na	1.92
		150	na	1.64	na	1.70
		180	na	1.51	na	1.51
		210	na	0.58	na	1.19
		240	na	1.11	na	1.59

Table Ap.IX.28. TIM-1 total phosphatidylcholine data (mM)

TIM-1 compartment	Sample Phase	Time (min)	Lab # 1 – Phase I		Lab # 1 – Phase II	
			1	2	1	2
Antrum	Total sample	15	3.29	2.19	2.34	2.81
		75	2.54	1.72	2.39	2.51
		135	1.28	1.45	2.21	2.10
		180	1.02	1.54	1.47	0.54
Duodenum	Total sample	30	5.26	na	3.34	na
		60	5.55	na	2.73	na
		90	5.19	na	4.32	na
		120	3.06	na	1.59	na
		150	2.91	na	3.48	na
		180	3.39	na	3.71	na
		210	3.74	na	4.26	na
		240	3.51	na	3.27	na
	Micellar phase	30	6.07	na	5.56	na
		60	3.34	na	4.20	na
		90	2.27	na	1.60	na
		120	2.27	na	1.46	na
		150	2.62	na	1.48	na
		180	3.12	na	3.41	na
		210	3.70	na	3.19	na
		240	3.26	na	2.63	na
Jejunum	Total sample	30	na	3.53	na	2.44
		60	na	4.04	na	4.61
		90	na	3.10	na	3.67
		120	na	2.76	na	2.76
		150	na	2.56	na	2.77
		180	na	2.41	na	2.73
		210	na	2.37	na	2.43
		240	na	1.99	na	2.41
	Micellar phase	30	na	3.06	na	3.17
		60	na	3.82	na	4.09
		90	na	2.59	na	3.55
		120	na	2.21	na	2.49
		150	na	2.03	na	2.15
		180	na	1.87	na	1.86
		210	na	0.89	na	1.55
		240	na	1.41	na	1.90