This is a peer-reviewed, accepted author manuscript of the following research article: Stamatopoulos, K., O'Farrell, C., Simmons, M., & Batchelor, H. (2021). In vivo models to evaluate ingestible devices: present status and current trends. *Advanced Drug Delivery Reviews*, *177*, [113915]. https://doi.org/10.1016/j.addr.2021.113915

In vivo models to evaluate ingestible devices: present status and current trends

Konstantinos Stamatopoulos[1,2], Connor O'Farrell[1], Mark Simmons[1], Hannah Batchelor[3*]

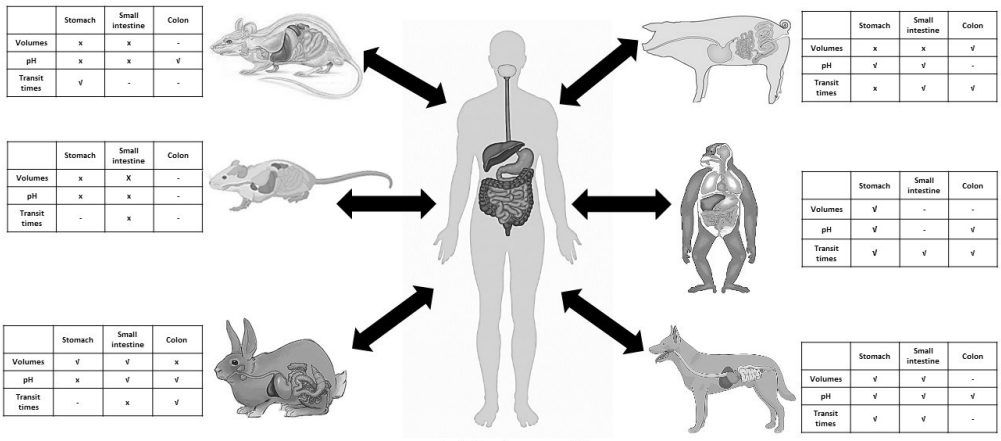
*Corresponding author

1. School of Chemical Engineering, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
2. Biopharmaceutics, Pharmaceutical Development, PDS, MST, RD Platform Technology & Science, GSK, David Jack Centre, Park Road, Ware, Hertfordshire, SG12 0DP, UK
3. Strathclyde Institute of Pharmacy and Biomedical Sciences, 161 Cathedral Street, Glasgow G4 0RE

1 Abstract

Evaluation of orally ingestible devices is critical to optimize their performance early in development. Using animals as a pre-clinical tool can provide useful information on functionality, yet it is important to recognize that animal gastrointestinal physiology, pathophysiology and anatomy can differ to that in humans and that the most suitable species needs to be selected to inform the evaluation. There has been a move towards in vitro and in silico models rather than animal models in line with the 3Rs (Replacement, Reduction and Refinement) as well as the better control and reproducibility associated with these systems. However, there are still instances where animal models provide the greatest understanding.

This paper provides an overview of key aspects of human gastrointestinal anatomy and physiology and compares parameters to those reported in animal species. The value of each species can be determined based upon the parameter of interest from the ingested device when considering the use of pre-clinical animal testing.



√ Suitability/comparable

Keywords: In vivo model; stomach; small intestine; colon; pre-clinical species

2 Introduction

Animals are used as pre-clinical models to evaluate the therapeutic index, toxicity and linear/non-linear pharmacokinetics of a drug, guiding human dose and formulation development. In general, small animals (rats, mice, guinea pigs and rabbits) are suitable for determining bioavailability and the mechanism of drug absorption, typically, from suspensions or solutions, while larger animals (dogs, pigs and monkeys) are used to evaluate absorption from formulations.

However, due to anatomical, physiological and metabolic differences between animals and humans, no single animal species provides an adequate physiological paradigm for the human environment [1]. Instead, the selection of the appropriate animal model used to extrapolate drug behaviour to humans depends on the mechanism of absorption and/or metabolism of the drug. Hence, microbiota composition will be the main factor to be considered when an animal model is selected to assess drug metabolism, including potential enterohepatic circulation of its metabolites, and/or the performance of microbial-triggered dosage forms. However, the animal model might differ when transit time is the important factor for an extended/sustained release formulation. This is also applied when the osmotic pressure of the lumen is the main factor that will affect the performance of an osmotic pump formulation.

A similar approach should be followed for the development of ingestible devices. For instance, considering the current size of ingestible devices, small animals (for example, rats) are unsuitable. The diameter of the small intestine in rats is 0.3 – 0.5 cm [2], whereas the diameter of different ingestible devices ranges between 1.08 – 1.3 cm [3]. In addition to any difficulty in swallowing the device or fatal damage to the GI tract of the animal due to such a large size, the device will alter motility and hence transit times and not be representative of the human in vivo environment. However, advances in technology permit smaller devices and as such small animals may have value in their evaluation [4]. Currently, wireless capsule technology has been validated for gastric and

small intestinal transit times in dogs [5-8], pigs [9], rabbits [10] and horses [11], but only single studies have used this technology for determining colonic transit times in dogs [6] and rabbits [10].

When considering ingestible devices for screening and diagnosis, the animal model suitable for developing the proper wireless device will be based on similarities in disease pathophysiology to human beings. The use of the most suitable model is critical to extrapolate the pre-clinical data to inform the design of the device and to enable translation into clinical use. Key factors to consider in the applicability of animal models in the evaluation of ingestible devices for screening and diagnosis include the anatomical shape of the organ, the motility and the transit time.

This review will describe the latest information on human anatomy and physiology as the basis against which the animal models are compared. The paper is subdivided into sections to represent the stomach, small intestine and large intestine.

3 The Stomach

The stomach is the first region within the GI tract where the ingested device will reside for a period of time. An understanding of the gastric environment is important to consider how the fluid volume; composition; motility and transit may affect the device under test.

3.1 Human gastric volume

The fluid volume within the stomach has previously been reviewed [12], however the total volume of the stomach or gastric capacity is different to the residual fluid within the human stomach. A summary of data on gastric capacity measurements in healthy adults is presented in Table 1.

Population	Technique	Volume (mL)			Reference
		Range	Mean	St. dev	
98 morbidly obese patients prior to gastrectomy	Multidetector computed tomography (MDCT) gastrography	800 - 1800	1310	307	[13]
20 deceased individuals of healthy BMI	Volume of saline required to fill the stomach	700 - 1600	1190	245	[14]
45 patients with BMI < 25 kg m^{-2}	3D CT gastrography following ingestion of effervescent granules to distend stomach with gas		438.5	163.4	[15]
4 lean subjects	Balloon inflated to		1100	185	[16]

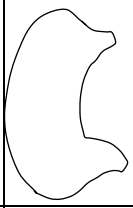
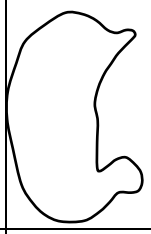
	measure capacity				

Table 1 Literature data on human gastric capacity.

There is some controversy in the literature about whether BMI is linked to gastric capacity; in some studies the correlation is significant yet the Pearson correlation coefficient was < 0.3 [13].

3.2 Animal stomach anatomy

When evaluating an ingestible device, the macroenvironment within the gastrointestinal tract is of importance; this can be related to the physical dimensions of the product under test to ensure that this can be accommodated within the stomach of the animal. The amount of fluid as well as total stomach capacity can be of interest to determine the dosing conditions for the ingested device. Other features of the stomach are of importance depending upon the function of the device under test, for example, mucus thickness. The relative shape of the stomach as well as the dimensions of the pyloric sphincter will affect the transit through the stomach of the animal in comparison to a human. Much of this data is summarized in Table 2 which compares the gastric anatomical and physiological conditions in relevant animal species to the human adult stomach.

Species	**Fasted fluid volume (mL)**	**Capacity [17, 18]**	**Mucus thickness (um)**	**Pyloric sphincter diameter (mm)**	**Shape**
Human (adult)	15-150 (see table in [12])	1000-1600 [17]		12.8	
Dog	24.0 ±4.2mL[19]	1000 [17] 4330 (Beagle) [20]	425 - 576 [18]	More restrictive than humans [21] 10-20 [20]	
Mini-pig	@15kh = 32.51 ± 4.19 mL @30kh = 78.87 ± 6.26 mL @50kh = 162.20 ± 8.39 mL[22]				

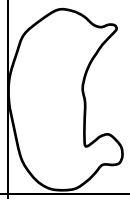
Pig	278 ± 186 [23]	6000 - 8000 [17]	190 - 222 [18]		
Monkey	100 [23]	100 [17]			
Rabbit	54.6 ± 16.2[23]		155 - 277 [18]	8 [20]	
Rat	2.29 ± 1.59 [23]	3.38 [18]	33 - 69 [18]	2 [20]	
Mouse	0.09 ± 0.07 [23]	0.37 [18]		0.25 [20]	
Guinea pig			234 - 473 [18]	5 [20]	

Table 2. Summary of anatomical and physiological aspects of animal and human stomach. Images are adapted from [17]; not to scale.

3.3 Gastric contents

The composition of human gastric fluids has previously been reviewed [12], however further detail on the gastric pH is of relevance here as this can be a critical factor to replicate when evaluating ingestible devices; particularly those that may be sensitive to prolonged exposure at low pH.

3.3.1 Human gastric pH

The harsh acidic conditions within the stomach are well known. There is extensive data on gastric pH throughout the literature. Table 3 shows the mean (and standard deviation of) gastric pH reported previously for both fed and fasted participants. The methodology used to assess pH and calorific load of the food ingested is also presented. The highest pH reported is in the fed state; typically, the peak pH is early in the post ingestion phase. As well as maximum pH values, the dynamic change in pH is of interest in simulating the stomach as well as regional differences in pH values. Often the percentage of time where the pH is greater than 4 is reported as this links to control in gastric reflux where a target for therapy is gastric pH > 4 [24]. Despite average pH values being recorded it is known that there are “spikes” in pH that occur and that the pH is not constant within the stomach; it is also known that there may be regions within the stomach where pH is lower due to the proximity to sources of acid secretion.

Method used to assess pH	Number of subjects	GI sub-location	Status	Calories ingested in the fed state	Mean pH	Standard deviation	Reference
Esophagogastric pH probe catheter	10	Proximal stomach	Fasted	0	1.47	0.15	[25]
Esophagogastric pH probe catheter	10	Proximal stomach	Fasted	0	1.83	0.27	[25]
Esophagogastric pH probe catheter	10	Proximal stomach	Fasted	0	2.04	0.24	[25]
Aspiration of GI fluids	24	Proximal stomach	Fasted	0	2.9	1.97	[26]
Two combined glass electrodes (Radiometer GK2802C)	7	Proximal stomach	Fasted	0	1.9	0.39	[27]
Esophagogastric pH probe catheter	10	Proximal stomach	Fasted	0	1.12		[28]
Esophagogastric pH probe catheter	10	Mid/distal stomach	Fasted	0	1.29	0.23	[25]
Esophagogastric pH probe catheter	10	Mid/distal stomach	Fasted	0	1.56	0.13	[25]
Esophagogastric pH probe catheter	10	Mid/distal stomach	Fasted	0	1.43	0.23	[25]
IntelliCap	20	Mid/distal stomach	Fasted	0	2.7	0.8	[29]
Heidelberg capsule	24	Mid/distal stomach	Fasted	0	1.73*	0.14*	[30]
Heidelberg capsule	79	Mid/distal stomach	Fasted	0	1.33*	0.08*	[31]
Aspiration of GI fluids	165	Mid/distal stomach	Fasted	0	2.9	0.46	[32]
pH electrode fixed to Stomach body	19	Mid/distal stomach	Fasted	0	1.38*	0.07*	[33]

Radiotelemetry capsule	12	Mid/distal stomach	Fasted	0	1.66*	0.5*	[34]
Radiotelemetry capsule	13	Mid/distal stomach	Fasted	0	1.88*	0.81*	[35]
Two combined glass electrodes (Radiometer GK2802C)	7	Mid/distal stomach	Fasted	0	1.9	0.49	[27]
Radiotelemetry capsule	39	Mid/distal stomach	Fasted	0	1.49*	0.14*	[35]
Radiotelemetry capsule	4	Mid/distal stomach	Fasted	0	1.4	0.4	[36]
Bravo pH capsule	8	Mid/distal stomach	Fasted	0	1.6	0.7	[37]
Aspiration of GI fluids	22	Mid/distal stomach	Fasted	0	1.5	0.5	[38]
Esophagogastric pH probe catheter	10	Mid/distal stomach	Fasted	0	1.1		[28]
Esophagogastric pH probe catheter	10	Proximal stomach	Fed	800	4.21		[28]
Esophagogastric pH probe catheter	10	Proximal stomach	Fed	341.48	2.96	0.29	[25]
Esophagogastric pH probe catheter	10	Proximal stomach	Fed	570.48	4.16	0.27	[25])
Aspiration of GI fluids	19	Proximal stomach	Fed	750	6.36	0.33*	[39]
Esophagogastric pH probe catheter	10	Proximal stomach	Fed	954.94	4.92	0.44	[25]
Two combined glass electrodes (Radiometer GK2802C)	7	Proximal stomach	Fed	954.94	3.93	1.2	[27]
Esophagogastric pH probe catheter	10	Mid/distal stomach	Fed	800	3.58		[28]
Heidelberg capsule	24	Mid/distal stomach	Fed	1000	4.9*	0.21*	[30]

Heidelberg capsule	79	Mid/distal stomach	Fed	1000	4.77*	0.27*	[31]
Esophagogastric pH probe catheter	10	Mid/distal stomach	Fed	341.48	2.5	0.77	[25]
Esophagogastric pH probe catheter	10	Mid/distal stomach	Fed	570.48	3	0.45	[25]
Esophagogastric pH probe catheter	10	Mid/distal stomach	Fed	954.94	4.04	0.44	[25]
Two combined glass electrodes (Radiometer GK2802C)	7	Mid/distal stomach	Fed	954.94	5.66	0.99	[27]

*Table 3. Mean and standard deviation pH values recorded in healthy adults from the literature. Table adapted and updated from [40]. *Mean and standard deviation (SD) were estimated and reported from median and interquartile range (IQR) or from median and range, original calculations performed by [40]*

3.3.2 Gastric pH in Animals

When comparing the gastric pH between humans and animals it is important to consider both mean and time-based profiles of pH in both a fasted and fed state. As stated for the human data, the gastric pH is not constant but is subject to some variation and spikes in pH values. Similar profiles have been reported in animal models, of which the pH data is presented in Table 4. The table has included pH measurements collected using a range of devices, including ingestible devices; the data in this table can be compared to the data from humans presented in Table 3.

Species	**Method**	**Fed/fasted status**	**Mean**	**St dev**	**Reference**
Mouse	Aspiration of fluids following sacrifice	Fasted	4.04	0.2	[41]
Mouse	Aspiration of fluids following sacrifice	Fed	2.98	0.3	[41]
Rat	Aspiration of fluids following sacrifice	Fasted	3.90	1.0	[41]
Rat	Aspiration of fluids following sacrifice	Fed	3.20	1.0	[41]
Guinea pig	Aspiration of fluids following sacrifice	Fed	4.4 (fundus) 2.9 (antrum)		[42]
Rabbit	Aspiration of fluids following sacrifice	Fed	3.0 (fundus)		[42]

			1.6 (antrum)		
Pig (Landrace)	SmartPill® GI Monitoring system	Fasted	2.0 - 7.0 (range)		[43]
Pig (Yorkshire)	Heidelberg Radiotelemetry Capsule	Fasted	1.15 - 4.0 (range)		[44]
Pig	Aspiration of fluids following sacrifice	Fed	4.5 (fundus) 4.4 (antrum)		[42]
Dog (beagle)	Heidelberg Radiotelemetry Capsule	Fasted	1.5	0.04	[45]
Dog (beagle)	Bravo® pH capsule	Fasted	1.5 (median) IQR: 1.6 - 3.4		[46]
Dog (beagle)	Bravo® pH capsule	Fasted	2.03	0.59	[47]
Dog (beagle)	Gastric aspirate	Fasted	6.8 Range 2.7 - 8.3	0.2	[48]
Monkey (Cynomolgus)	Bravo® pH capsule	Fasted	1.97 Range 1.9 - 2.2	1.4	[49]

Table 4. Comparison of gastric pH measurements in a range of animal species.

A comparison of the gastric pH in humans and dogs was presented by Koziolek et al (2019) following ingestion of a meal. It was noted that the timing of the meal relative to the medicine is important when matching the pH profile in the stomach in dogs compared to humans to provide the best correlation [50]. The pig model showed duodeno-gastric reflux prior to gastric emptying where there were spikes of higher pH within the stomach in the three hours before gastric emptying [43]; this coupled with the much longer gastric residence time in pigs suggests that a dog is a better model of the gastric environment.

A comparison of pH data in the stomach of animals is presented in Figure 1 and Figure 2. Due to many papers showing total GI pH, it can be complicated to extract the actual gastric pH from certain studies. Hence, only data from pigs and dogs are available for the fasted state; however, the range of human values was presented in Table 5Table 3.

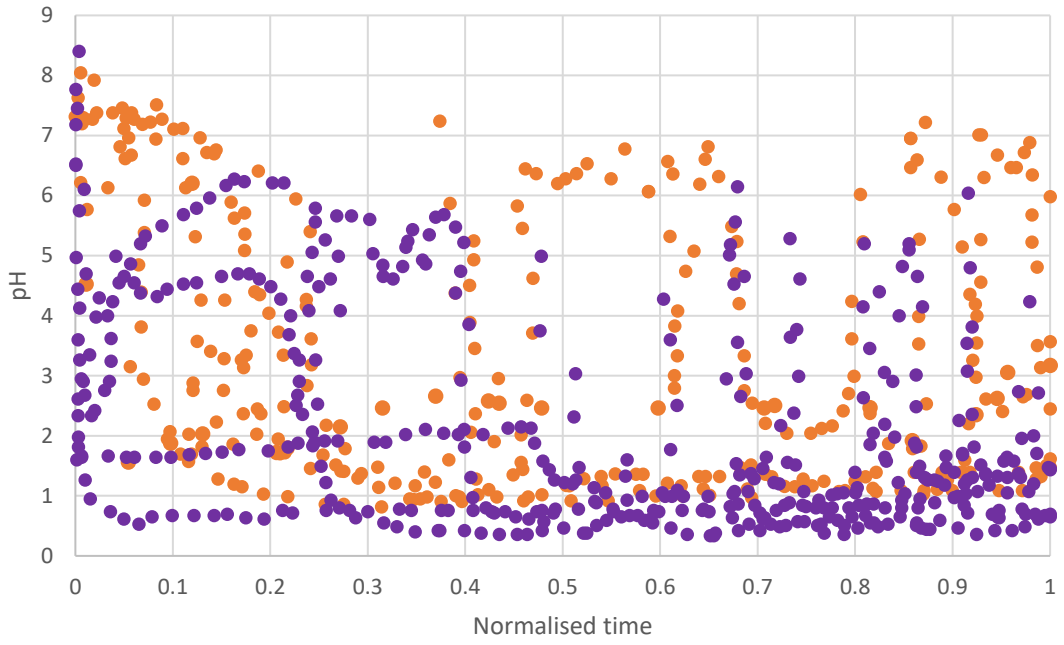


Figure 1. Comparison of gastric pH recorded using ingested devices in pigs (purple) [43] and dogs (orange) [50] in the fasted state.

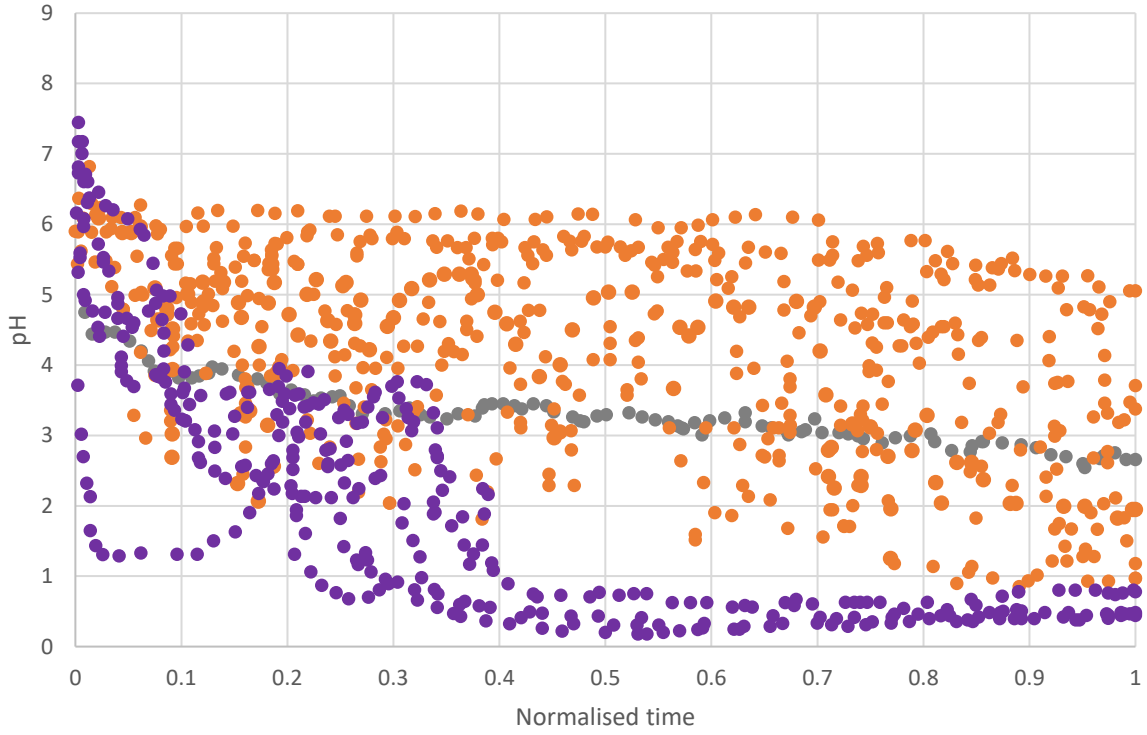


Figure 2. Comparison of gastric pH recorded using ingested devices in humans (grey) [51]; pigs (purple) [43] and dogs (orange) [50] in the fed state.

The variability in gastric pH is large in pigs and dogs yet this is likely to reflect the conditions in humans. In the fed state it should be noted that the gastric pH returns to low levels in pigs; this may be an artefact of the normalised *x* axis for time as gastric emptying was significantly longer in pigs compared to either humans or dogs.

Gastric pH is subject to variability influenced by diet and it is possible to use food or drugs to alter the pH within the stomach of animals and humans if required.

3.4 Gastric emptying

There is a significant difference between the emptying of liquid food and the emptying of solid food, and the emptying rate of liquids is faster than that of solids. The time taken to empty 50 % of the ingested contents ($t_{1/2}$) has often been used to describe gastric emptying rate for the purpose of comparison.

3.4.1 Gastric liquid emptying rate in humans

Crude measurements of gastric emptying were conducted in two males in 1977 by aspiration of the residual volume in the stomach following administration of a 250 mL volume via an intragastric tube [52]. The relative rate of emptying of water was compared to that of a suspension of barium sulphate in two healthy individuals where both fluids emptied at a similar rate; just 10% of the ingested volume remained after 15 minutes [52]. However, it is recognised that the presence of the gastric tube may affect physiology and gastric emptying. The use of ultrasound to measure gastric emptying was reported as a non-invasive technique that was used to measure gastric emptying of 500 mL of orange cordial [53]. Magnetic resonance imaging (MRI) was first reported as a tool to measure gastric emptying in 1992 [54]. The study used a liquid test meal consisting of 500 mL of a 10 % glucose solution containing contrast medium and ^{99m}Tc-DTPA to compare the MRI data to the detection of the fluid in the duodenum via a luminal duodenal tube [54].

Gastric emptying in relation to drug absorption has often considered in clinical scenarios where medicines are taken with a glass of water; this may be more relevant when considering ingestible medical devices. The gastric emptying time (gastric half-life) for a 240 mL volume of water when ingested following a 10 hour fast was reported to be 13.1 ± 1 minutes [55]. There was an initial increase to 242 mL after 2 minutes, but this declined rapidly to less than 50 mL by 45 minutes [55]. This finding was consistent with another study where the initial volume rose to 270 ± 20mL and subsequently decreased over time and at 90 minutes, when a second 240 mL volume of water was ingested, volume rose again to 251 ± 38 mL [56]. The gastric emptying rate constant for water was found to be between 0.10 - 0.15 min^{-1} [56]. Gastric volumes and gastric emptying rates of water when administered 30 minutes after three different meals were compared in a single center, 4-way crossover study [56]. A fasted control group was compared to groups fed a high-fat solid meal, a high-fat homogenous meal and a low-fat solid meal. The calorific content of the high- and low-fat meals was matched [56]. Shortly after consumption, gastric volumes were recorded to be 434 ± 31 mL after the high-fat meal, 336 ± 17 mL after the high-fat homogeneous meal, and 546 ± 48 mL after the low-fat solid meal [56]. The gastric emptying rate constants of water (k_e) were significantly higher in the case of the solid meals (> 1.5 min^{-1}) compared to the semisolid homogeneous meal (< 0.1 min^{-1}) [56]. This study suggests that the presence of food affects the gastric emptying of liquids and confirms the existence of the Magenstrasse (stomach road) phenomenon for three different meals [56]. Figure 3 compares the gastric emptying rate of liquids in human from published data, highlighting the variability in gastric emptying and how this can depend upon the composition and volume of fluid ingested, as well as the technique used for the measurement.

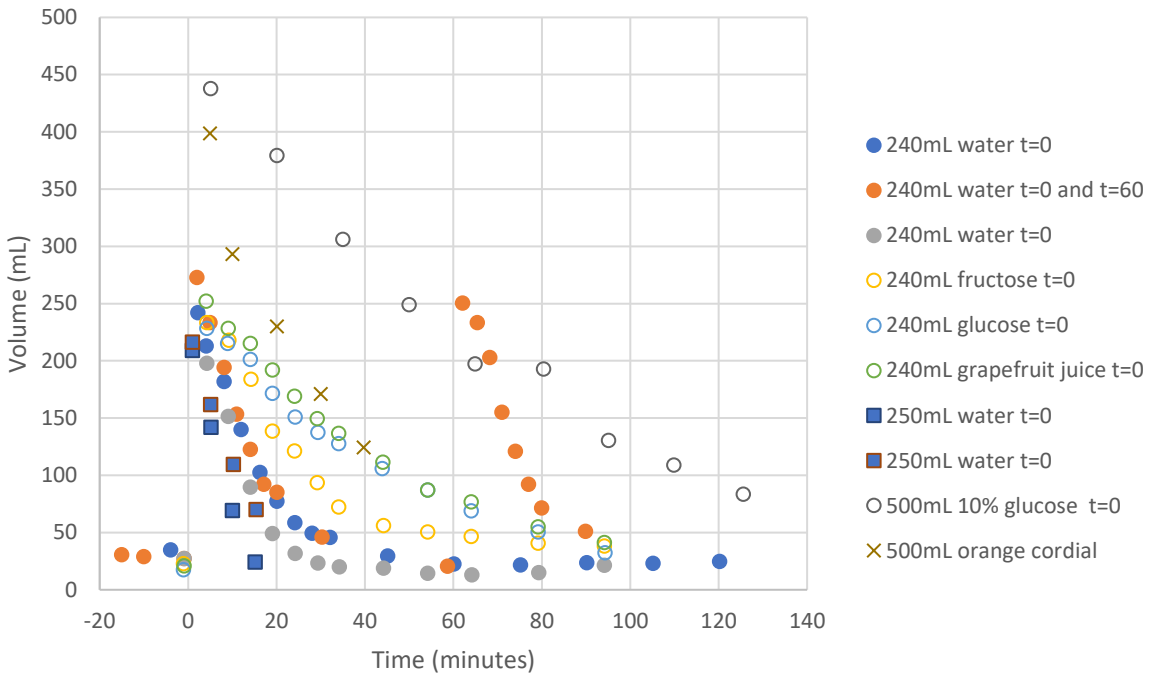


Figure 3. Comparison of the gastric emptying rate of liquids; the legend notes the volume and composition of the liquid ingested. The time of consumption of the fluid is noted in the legend for each liquid. The circles represent measurements taken with MRI, squares represent aspiration of fluids and 'x' corresponds to ultrasound. Data was extracted from [52-58].

3.4.2 Gastric solid emptying rate in humans

Gastric emptying of solids shows a biphasic pattern. In the first phase almost nothing is emptied, it is the delayed phase, where the solids are manipulated to form smaller particles and moved to the distal part of the stomach. The second phase is the linear emptying phase through the pylorus where small particles (less than 2 – 3 mm in size) are emptied in the digestive period that lasts 2 – 3 h after a meal. However, the stomach retains larger food particles that escape mincing during the digestive period, and then forcefully empties them into the small bowel during the inter-digestive period.

Gastric emptying of four homogenised meals (500 mL volume) of varying viscosity and nutrient content was evaluated using MRI [58] where it was found that increasing the nutrient content delayed gastric emptying, whereas increasing viscosity had a smaller effect. This was in agreement with a previous study that reported that the rate of emptying of food materials was based on calorific load with emptying controlled at rate (1 - 4 kCal min^{-1}) [59].

3.4.3 Gastric transit time in humans

Gastric transit time is influenced by many factors including fed status, caloric content of meal as well as measurement technique [60]. A summary of gastric transit times as a function of fasted / fed state and measurement technique for a range of oral solid dosage forms is presented in Table 5. The use of the solid dosage forms together with their size and density is of interest for ingested medical devices.

Method used	Number of	Formulation used	Fasted/fed status	Calories ingested	Transit time (hours)	Reference

	participants					in fed state			
		Dosage form	Diameter (mm)	Density (g cm^{-3})			Mean	Standard Deviation	
Gamma scintigraphy	8	Multiple-units	1.055	1.5	Fasted	0	0.5	0.4	[61]
Gamma scintigraphy	6	Multiple-units	1.16	1.5	Fasted	0	1.17	1.1	[62]
Gamma scintigraphy	8	Multiple-units	1.29	1.5	Fasted	0	3.08	2.13	[63]
Gamma scintigraphy	8	Multiple-units	1.29	2	Fasted	0	3.1	1.1	[63]
Gamma scintigraphy	8	Multiple-units	1.29	2.4	Fasted	0	2.8	1.52	[63]
Gamma scintigraphy	8	Multiple-units	0.5	1.5	Fasted	0	2.09	0.88	[64]
Gamma scintigraphy	8	Multiple-units	0.5	2.6	Fasted	0	2.36	1.03	[64]
Gamma scintigraphy	8	Multiple-units	4.75	1.5	Fasted	0	1.78	0.65	[64]
Gamma scintigraphy	8	Multiple-units	4.75	2.6	Fasted	0	2.13	0.94	[64]
Gamma scintigraphy	8	Multiple-units	0.5	1.25	Fed	669.22	3.6	1.2	[65]
Gamma scintigraphy	8	Multiple-units	0.95	1.2	Fed	286.81	2.52	1.35	[66]
Gamma scintigraphy	8	Multiple-units	1.055	1.5	Fed	717.02	1.3	0.3	[61]
Gamma scintigraphy	6	Multiple-units	1.16	1.5	Fed	535.37	3.02	0.69	[62]
Gamma scintigraphy	6	Multiple-units	0.95	1.5	Fed	358.51	1.75	0.77	[67]
Gamma scintigraphy	6	Multiple-units	0.95	1.2	Fed	358.51	1.98	0.61	[68]
Gamma scintigraphy	6	Multiple-units	0.95	1.2	Fed	860.42	4.75	1.84	[68]
Gamma scintigraphy	10	Multiple-units	1.055	1.81	Fed	358.51	1.65	0.33	[69]
AS Metal Detector System, Germany	6	Single-unit	6	1.4	Fasted	0	0.63	0.44	[70]
AS Metal Detector System, Germany	6	Single-unit	6	1.4	Fasted	0	0.63	0.32	[70]
Gamma scintigraphy	10	Single-unit	5	1.4	Fasted	0	0.78	0.54	[71]
Gamma scintigraphy	5	Multiple-units	5	1.4	Fasted	0	0.93	1.09	[72]
Gamma scintigraphy	6	Single-unit	8.2	1.44	Fasted	0	1.49	0.35	[73]
Magnetic Marker	6	Single-unit	11	1.4	Fasted	0	0.88	1.02	[74]

Monitoring									
Gamma scintigraphy	8	Single-unit	6.6	1.41	Fasted	0	1.3	0.84	[75]
Gamma scintigraphy	8	Single-unit	6.6	2.85	Fasted	0	1.93	1.23	[75]
Gamma scintigraphy	8	Single-unit	8	1.4	Fasted	0	1.05	0.77	[76]
Gamma scintigraphy	6	Single-unit	7.3	1.4	Fasted	0	1.2	0.42	[77]
Gamma scintigraphy	6	Single-unit	4	1.4	Fasted	0	0.64	0.29	[78]
Gamma scintigraphy	6	Single-unit	4	1.4	Fasted	0	0.86	0.54	[78]
Radiotelemetry capsule	4	Single-unit	7	1.5	Fasted	0	1.9	1.1	[79]
Gamma scintigraphy	6	Single-unit	5	1.4	Fasted	0	0.45	0.19	[71]
Radiotelemetry capsule	8	Single-unit	5	1.4	Fasted	0	1.03	0.35	[76]
SmartPill capsule	5	Single-unit	11.7	1.4	Fasted	0	1.53	1.64	[80]
SmartPill capsule	10	Single-unit	13	1.4	Fasted	0	1.28	1.22	[81]
Heidelberg capsule	10	Single-unit	7	1.4	Fasted	0	1.93	0.42	[82]
SmartPill capsule	20	Single-unit	11	1.4	Fasted	0	0.84	0.68	[29]
IntelliCap	16	Single-unit	11	1.4	Fasted	0	1.45	0.93	[83]
Gamma scintigraphy	8	Single-unit	9	1.4	Fed	669.22	9.6	6.2	[65]
AS Metal Detector System, Germany	6	Single-unit	6	1.4	Fed	155.83	2.13	0.56	[70]
AS Metal Detector System, Germany	6	Single-unit	6	1.4	Fed	239.01	2.53	0.24	[70]
AS Metal Detector System, Germany	6	Single-unit	6	1.4	Fed	525.81	4.15	0.98	[70]
AS Metal Detector System, Germany	6	Single-unit	6	1.4	Fed	525.81	3.35	0.41	[70]
AS Metal Detector System, Germany	6	Single-unit	6	1.4	Fed	525.81	4.63	0.78	[70]
AS Metal Detector System, Germany	6	Single-unit	6	1.4	Fed	956.02	4.02	1.55	[70]
AS Metal Detector System, Germany	6	Single-unit	6	1.4	Fed	956.02	5.55	1.06	[70]
AS Metal Detector System, Germany	6	Single-unit	6	1.4	Fed	573.61	4.37	1.03	[70]

Gamma scintigraphy	3	Multiple-units	3	1.4	Fed	358.51	1.9	0.72	[72]
Gamma scintigraphy	3	Multiple-units	4	1.4	Fed	358.51	1.1	0.4	[72]
Gamma scintigraphy	3	Multiple-units	5	1.4	Fed	358.51	1.25	0.09	[72]
Gamma scintigraphy	3	Multiple-units	3	1.4	Fed	836.52	3.22	0.87	[72]
Gamma scintigraphy	3	Multiple-units	4	1.4	Fed	836.52	2.58	1.73	[72]
Gamma scintigraphy	3	Multiple-units	5	1.4	Fed	836.52	3.53	0.64	[72]
Gamma scintigraphy	6	Multiple-units	5	1.4	Fed	549.71	2.58	0.65	[72]
Gamma scintigraphy	6	Multiple-units	6	1.4	Fed	549.71	2.7	0.94	[72]
Gamma scintigraphy	6	Multiple-units	7	1.4	Fed	549.71	2.08	1.43	[72]
Gamma scintigraphy	10	Single-unit	5	1.4	Fed	512.91	2.36	0.7	[71]
Gamma scintigraphy	6	Single-unit	8.2	1.44	Fed	956.02	4.66	1.74	[73]
Magnetic Marker Monitoring	4	Single-unit	11	1.4	Fed	669.22	3.5	0.58	[74]
Gamma scintigraphy	6	Single-unit	11.5	1.4	Fed	358.51	1.5	0.52	[67]
Gamma scintigraphy	8	Single-unit	12	1.3	Fed	358.51	5.1	3.27	[84]
Gamma scintigraphy	8	Single-unit	12	1.3	Fed	717.02	7.65	2.93	[84]
Gamma scintigraphy	6	Single-unit	4	1.4	Fed	382.41	3	2.94	[78]
Gamma scintigraphy	6	Single-unit	4	1.4	Fed	382.41	3.3	2.03	[78]
Gamma scintigraphy	6	Single-unit	6	2.2	Fed	100.38	1.62	0.74	[85]
Gamma scintigraphy	6	Single-unit	6	2.2	Fed	100.38	1.52	0.43	[85]
Gamma scintigraphy	6	Single-unit	4	1.4	Fed	308	3.5	0.8	[79]
Gamma scintigraphy	8	Single-unit	8	1.4	Fed	669.22	2.67	1.32	[76]
Gamma scintigraphy	8	Single-unit	8	1.4	Fed	669.22	1.67	1.82	[76]
Radiotelemetry capsule	8	Single-unit	5	1.4	Fed	669.22	2.67	2.12	[76]
SmartPill capsule	15	Single-unit	11.7	1.4	Fed	255.02	4.35	1.42	[80]

Table 5. gastric transit time of ingested formulated products as a function of their size; density and the fed state of the participants. Data taken from [60]

3.4.4 Gastric residence time in animals

A comparative gastric residence time can be of great importance in the evaluation of ingestible devices. It has been reported that the gastric residence time in pigs far exceeds that reported in adults and as such the power supply for ingested devices can limit their functionality when evaluated in pig models. Table 6 shows the residence time of solid units as measured in animal models to provide an indication of the relative gastric residence time.

Species	**Method**	**Fasted/fed status**	**Calories ingested in the fed state**	**Mean (hours)**	**St dev**	**Reference**
Rat	Visual observation of sacrificed animal (transit of high density 1 mm pellets)	Fed	n/a	2.1	n/a	[86]
Dog (beagle)	X-ray visualisation of ingested pellets (0.3 - 1 mm and 1 – 1.7 mm diameter)	Fed	n/a	6 - 8 hours	n/a	[87]
Dog (beagle)	Heidelberg Radiotelemetry Capsule	Fasted	n/a	1.2	0.33	[45]
Dog (beagle)	Bravo® pH capsule	Fasted	n/a	0.41 (median)		[46]
Dog (beagle)	Bravo® pH capsule	Fasted	n/a	1.39	1.39	[47]
Dog (beagle)	SmartPill® GI Monitoring system	Fasted	n/a	0.57	0.37	[50]
Dog (beagle)	SmartPill® GI Monitoring system	Fed	11.3 kcal kg^{-1} body weight	2.94	0.91	[50]
Pig (Landrace)	SmartPill® GI Monitoring system	Fasted	n/a	121.75	75	[43]
Pig (Yorkshire)	Heidelberg Radiotelemetry Capsule	n/a	n/a	> 144		[44]
Pig (Landrace)	SmartPill® GI Monitoring system	Fed	444	50.51	45	[43]

Minipig (Yucatan)	Heidelberg Radiotelemetry Capsule	Fasted (in early phase after dosing)		6.3	1.6	[88]
Minipig (Yucatan)	Heidelberg Radiotelemetry Capsule	Fasted (in later phase (20 min-4 hours) after dosing)	n/a	1.3	0.7	[88]
Monkey (Cynomolgus)	Bravo® pH capsule	Fasted	n/a	2.55	1.45	[49]

Table 6. Comparison of the gastric residence time reported in animal models using ingested devices. n/a: not available.

The size shape and density of the ingested material has been shown to influence the gastric emptying time in rats [86]; dogs [87] and humans [21]. The relative gastric transit needs to be considered when using an animal to evaluate an ingested device.

3.4.5 Pyloric sphincter in animals

The pyloric sphincter can control transit from the stomach to the small intestine, in humans it has been reported that particles larger than 2 mm diameter are unable to pass through the pyloric sphincter where the diameter is 2.5 - 5 cm [20]. The diameter of the pyloric sphincter in a range of animals has been reported with values of 1 - 2 cm for a Beagle dog; 8 mm for a rabbit; 5mm for a guinea pig and estimated values of 0.25 mm for a mouse and 2mm for a rat [20].

3.5 Gastric pressures/motility

Normal motility in the human adult stomach differs in the fasted and fed state to account for the function of the stomach. There is also a difference in motility within the stomach depending upon the anatomy, the proximal part acts as a reservoir and the antral part as a pump. The reservoir part of the stomach can expand upon the ingestion of food without a significant increase in intraluminal pressure. The antral part of the stomach exhibits phasic contractions to mix and breakdown food prior to passage to the small intestine via the pyloric sphincter.

The migrating motor complex (MMC) describes the contractile activity in the stomach (and remainder of the intestine). The total duration of the MMC in humans has been reported to be 172 ± 76 minutes [89]. The MMC consists of three phases: phase I is a period of no contractions; phase II is irregular contractions and phase III is regular high amplitude contractions; defined as regular contractions for at least 2 minutes with 2 - 3 contractions per minute [90]. The ingestion of food can interrupt the MMC cycle.

The dominant phase of the MMC in the stomach was phase I which was present for more than half of the duration of the MMC [89]. The duration of phase III activity in the stomach was reported to be 3.6 ± 1.1 minutes and 3.8 ± 1.7 minutes in the proximal and distal positions within the stomach in fasted adults with mean frequencies of 2.7 ± 0.3 and 2.9 ± 0.2 respectively [89]. The mean amplitude of a phase III contraction is 75 mg Hg in the stomach [90].

3.5.1 Gastric pressures and motility in animals

Pressures reported in the stomach have included values of up to 800 mbar in dogs (typical range 500 - 800 mbar) [50]; were up to 402 mbar in the stomach with an average of 349 ± 84 mbar under fasted conditions, and 250 ± 103 mbar in the fed state in pigs (Landrace) [43].

The strength of gastric contractions in dogs measured using an ingested sensor reported maximum amplitude contractions ranging from 13 - 94mmHg with a frequency of 3.7 contractions per minute [8].

The gastric emptying force has been compared in dogs and humans using pressure sensitive tablets where the area area-normalized gastric emptying force (dynes cm^{-2}) was 606 and 3858 in fasted humans and dogs with values of 962 and 3639 dynes cm^{-2} for fed humans and dogs respectively [91]. Other work has compared the mechanical destructive force in the stomach of dogs and humans with values of 3.2 N and 1.9 N being reported respectively [92].

Further work is required to compare data on gastric pressures and motility in animal species and humans to better understand the similarities and differences to enable selection of the most appropriate species.

4 The Small Intestine (SI)

The human small intestine extends from the pylorus at the exit of the stomach to the beginning of the colon. The duodenum is the first part of the small intestine, with an average length of 25 cm, approximately in line with the length of its Latin definition “12 fingers” [93]. The jejunum and ileum make up the remainder of the small intestine and are reported to measure 5 – 8 m in length, where the jejunum represents the proximal 40 % and the ileum the distal 60 % [94, 95]. However, the length of the small intestine varies with the degree of longitudinal smooth muscle contraction and the method used for assessment [96, 97]. A comparison of the dimensions of the small intestine between humans and animals is provided in Table 7.

	Length (m)					
Species	**Overall**	**Duodenum**	**Jejunum**	**Ileum**	**Diameter (cm)**	**Capacity (L)**
Rats	1.2 - 1.7	0.95 - 1	9 - 1.35	0.25 - 0.35	0.3 - 0.5	
Mouse	0.35 - 0.45 [17]					
Rabbit	3.56 [17]	41.26 [98]	106.6 [98]	21.64 [98]	7.71 [98]	
Dog	4.14 [17]	0.25 [17]		0.15 [17]	1.0	1.62
Monkey					1.2 - 2	
Pig	18.29 [17]				2.5 - 3.5	33.5

Guinea pig	0.15 [99]					
Horse	22.44 [17]					63.82
Ox	46.00 [17]					66.0
Human	5 - 8	0.25 [93]	2-3 [94, 95]	3 – 4.5 [94, 95]	2.5	

Table 7. Comparison of the reported dimension of the small intestine in a range of animals.

Arrangement is less meaningful for SI compared to the stomach as it is the overall length and diameter that are of interest. The length of the small intestine relative to the size of the animal has previously been explored to link the absorptive capacity to the nutrient requirements. The overall absorptive capacity of the small intestine is also a function of the surface area; the villi and microvilli in humans greatly extends the surface area compared to the basic anatomical length and diameter.

4.1 Small intestinal pH

There is extensive data on human small intestinal pH within the literature [60]. Table 8 shows the mean (and standard deviation) small intestinal pH reported previously in the literature for both fed and fasted participants. The methodology used to assess pH and calorific load of the food ingested is also presented. Often the trigger to signal that the ingested device is within the small intestine is a change in pH and the pH changes with location. As with the stomach the pH profile is not constant, fluctuating between pH6 to pH 7-8 [100] although fewer spikes in pH are observed in the small intestine compared to the stomach.

Method	Number of participants	GI sub-location	Fed/fasted Status	Calories ingested in the fed state	pH value		Reference
					Mean	SD	
Beckman Cecar miniature combined pH electrode	8	Duodenal bulb	Fasted	0	6.81	0.67	[101]
SmartBill GI monitoring system	10	Duodenal bulb	Fasted	0	5.61	0.49	[81]
Beckman Cecar miniature combined pH electrode	8	Duodenal bulb	Fed	1147	6.12	0.6	[101]
pH electrode (GK 282c, Radiometer)	8	Duodenal bulb	Fed	954.94	5.3	0.9	[102]

pH electrode (GK 282c, Radiometer)	8	Duodenal bulb	Fed	954.94	5.2	1.1	[102]
Heidelberg capsule	79	Mid/distal duodenum	Fasted	0	6.47*	0.08*	[31]
Heidelberg capsule	22	Mid/distal duodenum	Fasted	0	6.13*	0.1*	[30]
pH electrode (GK 282c, Radiometer)	8	Mid/distal duodenum	Fasted	0	6.3	0.9	[102]
Heidelberg capsule	10	Mid/distal duodenum	Fasted	0	5.7	0.61*	[82]
Heidelberg capsule	79	Mid/distal duodenum	Fed	1000	6.53*	0.05*	[31]
Heidelberg capsule	22	Mid/distal duodenum	Fed	1000	6*	0.16*	[30]
Aspiration of GI fluids	15	Mid/distal duodenum	Fed	750	6.61	0.27*	[39]
Heidelberg capsule	6	Mid/distal duodenum	Fasted	954.94	5.8	0.8	[79]
Radiotelemetry capsule	39	Mid/distal duodenum	Fed	954.94	6.36*	0.23*	[35]
IntelliCap	20	Proximal small intestine	Fasted	0	6	0.2	[100]
Radiotelemetry capsule	55	Proximal small intestine	Fasted	0	6.63	0.53	[103]
Aspiration of GI fluids	24	Proximal small intestine	Fasted	0	7.1	0.6	[26]
SmartBill GI monitoring system	10	Proximal small intestine	Fasted	0	6.2	0.33	[81]
Radiotelemetry capsule	12	Proximal small intestine	Fasted	0	6.74*	0.37*	[34]
Radiotelemetry capsule	13	Proximal small intestine	Fasted	0	6.38*	0.27*	[104]
Radiotelemetry capsule	39	Proximal small intestine	Fasted	954.94	6.63*	0.17*	[35]
Radiotelemetry capsule	7	Proximal small intestine	Fasted	954.94	6.6	0.5	[105]
Radiotelemetry capsule	4	Proximal small intestine	Fasted	954.94	6.8	0.4	[36]

Bravo pH capsule	8	Proximal small intestine	Fasted	954.94	6.2	0.2	[76]
Radiotelemetry capsule	4	Proximal small intestine	Fed	954.94	5.88*	0.81*	[106]
Radiotelemetry capsule	52	Mid small intestine	Fasted	0	7.41	0.36	[103]
SmartBill GI monitoring system	10	Mid small intestine	Fasted	0	6.68	0.32	[81]
Radiotelemetry capsule	13	Mid small intestine	Fasted	0	7.17*	0.39*	[104]
Radiotelemetry capsule	39	Mid small intestine	Fasted	954.94	7.01*	0.16*	[35]
Bravo pH capsule	8	Mid small intestine	Fasted	954.94	6.7	0.4	[76]
Radiotelemetry capsule	10	Mid small intestine	Fed	954.94	6.72*	0.42*	[106]
IntelliCap	20	Distal small intestine	Fasted	0	7.7	0.15	[100]
Radiotelemetry capsule	58	Distal small intestine	Fasted	0	7.49	0.46	[103]
SmartBill GI monitoring system	10	Distal small intestine	Fasted	0	6.88	0.2	[81]
Radiotelemetry capsule	12	Distal small intestine	Fasted	0	7.42*	0.33*	[34]
Radiotelemetry capsule	13	Distal small intestine	Fasted	0	7.38*	0.45*	[104]
Radiotelemetry capsule	39	Distal small intestine	Fasted	954.94	7.28*	0.09*	[35]
Radiotelemetry capsule	7	Distal small intestine	Fasted	954.94	7.4	0.4	[105]
Radiotelemetry capsule	4	Distal small intestine	Fasted	954.94	7.7	0.2	[36]
Bravo pH capsule	8	Distal small intestine	Fasted	954.94	7.4	0.3	[76]
Radiotelemetry capsule	11	Distal small intestine	Fed	954.94	7.55*	0.5*	[106]

*Table 8. Mean and standard deviation pH values recorded in healthy adults from the literature. Table adapted and updated from [18]. *Mean and standard deviation (SD) were estimated and reported from median and interquartile range (IQR) or from median and range, original calculations performed by [40]*

Data on small intestinal pH is complex as it relies on accurate measurement of transit from the stomach into the small intestine. Data is available on the pH values in the small intestine of pigs in both the fasted and fed state [43], however due to the long gastric emptying time of > 8 hours it is questionable whether the fed state affects small intestinal pH in pigs. Overall pH values ranged from pH 6 - 8 in the small intestine of a Landrace pig [43].

Small intestinal pH in animals has been measured using ingested devices; the transit from stomach to small intestine is often noted as a change in pH and thus the recording is initiated at this point. A summary of pH data reported from the small intestine of animals is presented in Table 9.

Species	Method	GI sub-location	Fed/fasted status	Mean pH	St dev	Reference
Mouse	Aspirated fluids following sacrifice	Duodenum	Fasted	4.74	0.3	[41]
Mouse	Aspirated fluids following sacrifice	Duodenum	Fed	4.87	0.3	[41]
Mouse	Aspirated fluids following sacrifice	Jejunum	Fasted	5.01	0.3	[41]
Mouse	Aspirated fluids following sacrifice	Jejunum	Fed	4.82	0.2	[41]
Mouse	Aspirated fluids following sacrifice	Ileum	Fasted	5.24	0.2	[41]
Mouse	Aspirated fluids following sacrifice	Ileum	Fed	4.81	0.3	[41]
Rat	Aspirated fluids following sacrifice	Duodenum	Fasted	5.89	0.3	[41]
Rat	Aspirated fluids following sacrifice	Duodenum	Fed	5.00	0.3	[41]
Rat	Aspirated fluids following sacrifice	Jejunum	Fasted	6.13	0.3	[41]
Rat	Aspirated fluids following sacrifice	Jejunum	Fed	5.10	0.4	[41]
Rat	Aspirated fluids following sacrifice	Ileum	Fasted	5.93	0.4	[41]
Rat	Aspirated fluids following sacrifice	Ileum	Fed	5.90	0.4	[41]
Guinea-pig	Aspirated fluids following sacrifice	Proximal SI	Fed	6.85		[42]
Guinea-pig	Aspirated fluids following sacrifice	Mid SI	Fed	7.3		[42]

Guinea-pig	Aspirated fluids following sacrifice	Distal SI	Fed	7.35		[42]
Rabbit	Aspirated fluids following sacrifice	Proximal SI	Fed	6.8		[42]
Rabbit	Aspirated fluids following sacrifice	Mid SI	Fed	7.0		[42]
Rabbit	Aspirated fluids following sacrifice	Distal SI	Fed	7.2		[42]
Dog (beagle)	SmartPill® GI Monitoring system	Small Intestine proximal	Fasted	6.5-7.0 (range)		[50]
Dog (beagle)	SmartPill® GI Monitoring system	Small Intestine distal	Fasted	7.5-8.0 (range)		[50]
Dog (beagle)	Heidelberg Radiotelemetry Capsule	Small intestine	Fasted	6.1	0.1	[107]
Pig (Landrace)	SmartPill® GI Monitoring system	Duodenum	Fasted	6.7-7.5 (range)		[43]
Pig (Landrace)	SmartPill® GI Monitoring system	Ileum	Fasted	6.3-7.9 (range)		[43]
Pig	Aspirated fluids following sacrifice	Proximal SI	Fed	6.1-6.4 (range)		[42, 50]
Pig	Aspirated fluids following sacrifice	Mid SI	Fed	6.3-6.4 (range)		[42, 50]
Pig	Aspirated fluids following sacrifice	Distal SI	Fed	6.4-6.7 (range)		[42]

Table 9. Comparison of small intestinal pH measurements in a range of animal species

The pH in the small intestine showed a narrower distribution compared to that in the stomach; most likely due the reflux that is observed in the stomach and not observed within the small intestine. Most of the animal data shows similar pH values to the human although the data from mice and rats is lower compared to other animals and humans.

4.2 Small intestinal transit time in humans

The transit through the small intestine can be complex to measure as invasive methods are required to define the start and end points. Techniques used to measure small intestinal transit range from imaging techniques to ingestion of devices that report the pH over time and can thus be used to measure the total small intestinal transit time. A summary of the literature reports on small

intestinal transit time together with the method used to measure this in humans is presented in Table 10. The data shows the shortest transit times are less than 2 hours and the longest are close to 5 hours. The method used to measure transit as well as dimensions and density of the object under test can influence the transit through the small intestine.

				Transit time (h)				
Method	Dosage form	Prandial status	Calories	Mean	SD	Diameter (mm)	Density (g/cm3)	References
Gamma scintigraphy	Multiple-units	Fasted	0	3.7	1.6	1.055	1.5*	[61]
Gamma scintigraphy	Multiple-units	Fasted	0	4.17	1.18	1.16	1.5*	[62]
Gamma scintigraphy	Multiple-units	Fasted	0	4.52	1.35	1.29	1.5	[63]
Gamma scintigraphy	Multiple-units	Fasted	0	4.38	1.43	1.29	2	[63]
Gamma scintigraphy	Multiple-units	Fasted	0	3.4	1.11	1.29	2.4	[63]
Gamma scintigraphy	Multiple-units	Fasted	0	2.74	1.01	0.5	1.5	[64]
Gamma scintigraphy	Multiple-units	Fasted	0	3.09	1.12	0.5	2.6	[64]
Gamma scintigraphy	Multiple-units	Fasted	0	3.16	0.8	4.75	1.5	[64]
Gamma scintigraphy	Multiple-units	Fasted	0	4.01	1.8	4.75	2.6	[64]
Gamma scintigraphy	Multiple-units	Fed	669.22	3.1	1.4	0.5	1.25*	[65]
Gamma scintigraphy	Multiple-units	Fed	717.02	3.2	1.1	1.055	1.5*	[61]
Gamma scintigraphy	Multiple-units	Fed	535.37	3.9	0.98	1.16	1.5*	[62]
Gamma scintigraphy	Multiple-units	Fed	358.51	3.48	1.01	0.95	1.5*	[67]
Gamma scintigraphy	Multiple-units	Fed	358.51	3.13	1.14	0.95	1.2	[68]
Gamma scintigraphy	Multiple-units	Fed	860.42	3.37	1.14	0.95	1.2	[68]
Gamma scintigraphy	Multiple-units	Fed	358.51	3.4	1.46	1.055	1.81	[69]
Gamma scintigraphy	Single-unit	Fasted	0	3.64	0.67	5	1.4*	[71]
Gamma scintigraphy	Multiple-units	Fasted	0	3.17	1.44	5	1.4*	[72]
Gamma scintigraphy	Single-unit	Fasted	0	3.12	0.66	8.2	1.44	[73]
Magnetic Marker Monitoring	Single-unit	Fasted	0	3.2	1.25	11	1.4*	[74]

Gamma scintigraphy	Single-unit	Fasted	0	2.32	1.02	8	1.4*	[76]
Gamma scintigraphy	Single-unit	Fasted	0	4.08	0.25	7.3	1.4*	[77]
Gamma scintigraphy	Single-unit	Fasted	0	3	1.22	4	1.4*	[78]
Gamma scintigraphy	Single-unit	Fasted	0	3.3	1.81	4	1.4*	[78]
Radiotelemetry capsule	Single-unit	Fasted	0	3.75	1.67	5	1.4*	[76]
SmartPill capsule	Single-unit	Fasted	0	3.32	1.37	13	1.4*	[81]
SmartPill capsule	Single-unit	Fasted	0	4.62	1.98	11	1.4*	[51]
IntelliCap	Single-unit	Fasted	0	4	1.08	11	1.4*	[83]
Gamma scintigraphy	Single-unit	Fed	669.22	2	1	9	1.4*	[65]
Gamma scintigraphy	Multiple-units	Fed	358.51	2.32	0.4	3	1.4*	[108]
Gamma scintigraphy	Multiple-units	Fed	358.51	2.68	0.52	4	1.4*	[108]
Gamma scintigraphy	Multiple-units	Fed	358.51	3.67	0.64	5	1.4*	[108]
Gamma scintigraphy	Multiple-units	Fed	836.52	3.25	0.14	3	1.4*	[108]
Gamma scintigraphy	Multiple-units	Fed	836.52	2.83	1.53	4	1.4*	[108]
Gamma scintigraphy	Multiple-units	Fed	836.52	2.2	0.38	5	1.4*	[108]
Gamma scintigraphy	Multiple-units	Fed	549.71	3.05	1.47	5	1.4*	[108]
Gamma scintigraphy	Multiple-units	Fed	549.71	2.93	0.98	6	1.4*	[108]
Gamma scintigraphy	Multiple-units	Fed	549.71	2.85	1.22	7	1.4*	[108]
Gamma scintigraphy	Single-unit	Fed	512.91	3.55	0.47	5	1.4*	[71]
Gamma scintigraphy	Single-unit	Fed	956.02	3.16	0.36	8.2	1.44	[73]
Gamma scintigraphy	Single-unit	Fed	358.51	3.03	1.1	11.5	1.4*	[67]
Gamma scintigraphy	Single-unit	Fed	358.51	2.83	1.41	12	1.3	[84]
Gamma scintigraphy	Single-unit	Fed	717.02	3.15	2.25	12	1.3	[84]
Gamma scintigraphy	Single-unit	Fed	382.41	3.2	1.37	4	1.4*	[78]
Gamma scintigraphy	Single-unit	Fed	382.41	3.4	1.37	4	1.4*	[78]

Gamma scintigraphy	Single-unit	Fed	669.22	2.4	1.3	8	1.4*	[76]
Gamma scintigraphy	Single-unit	Fed	512.91	1.91	0.47	5	1.4*	[76]
Gamma scintigraphy	Single-unit	Fed	669.22	1.77	0.72	8	1.4*	[76]
Radiotelemetry capsule	Single-unit	Fed	669.22	2.83	1.37	5	1.4*	[76]
Gamma scintigraphy	Single-unit	Fed	100.38	5.33	1	6	2.2	[85]
SmartPill capsule	Single-unit	Fed	260	4.81	0.88	13	1.4*	[109]

Table 10. Small intestinal transit time of ingested formulated products as a function of their size; density and the prandial state of the participants. Data taken from [60]

4.3 Small intestinal transit time in animals

Data on small intestinal transit can be difficult to measure in small animals. A summary of the small intestinal transit times from a range of animals is presented in Table 11.

	Region	**Rat**	**Mice**	**Rabbit**	**Dog**	**Pig**	**Minipig**		
Status							suckling	3 days postweaning	2 weeks postwea
Fasted					111 ± 17 min[110]	3.0 - 4.0 [111]	1.5 - 3.5 [112]		
						4.3 [114]$^{s.p,LF}$	7 [112]		
						3.9 [114]$^{s.p,MF}$	9.5 [112]		6 [112]
						3.7 [114]$^{s.p,HF}$	28.5 [112]	4 - 28.0 [112]	12 [112]
						4.4 [114]$^{\cdot p,LF}$	30.5 [112]	30 [112]	15 [112]
						4.0 [114]$^{l.p,MF}$			
					1.37 ± 0.59[z]	3.9 [114]$^{l.p,HF}$			
Fed		25.1 [115]							
		21.4 [115]			1.9 [107]				
		3.3 [116]			1.85± 0.28 min[117]				
					1.94 ±0.27[50]				
					3.05 (1.53-4.83)[118]				
					7.12-42.88[7]				
	Jejunum	10 - 20 min [86]		10 - 20 min [119]					
	Ileum	30 - 60 min [86]		30 - 60 min [119]					

	Cecal arrival time	4.73 [86]							
		3.87 [86]							

Table 11. Small intestinal transit times reported in animal species (note that the units are hours unless otherwise stated).

4.4 Small intestinal contents

The composition of human small intestinal fluids has previously been reviewed [12], however a comparison of key parameters to those identified in animal intestinal fluids is presented in Table 12. It should be noted that there are simulated small intestinal fluids reported for rats [120]; dogs [121] and pigs [122].

Species	Volume (mL)	Osmolality ($mOsm \cdot kg^{-1}$)	Surface tension ($mN \cdot m^{-1}$)	Buffer capacity ($mmol \cdot L^{-1} \cdot pH^{-1}$)	References
Rats	3.89 ± 0.77	546 - 896	33 - 39	20 - 29	[18, 42, 123]
Mouse	0.31 ± 0.16	n/a	n/a	n/a	[18]
Rabbit	19.9 ± 4.5	475-541	39 - 42	25 - 37	[42, 123]
Dog	300	70 (fasted) 667 - 841 (fed)	30	1.4 (fasted) 24-30 (fed)	[39, 124]
Monkey	794	n/a	n/a	n/a	n/a
Pig	476 ± 253	439 - 492	33 - 44	20 - 28	[42, 123]
Guinea pig	n/a	292 – 326 [125]	n/a	n/a	n/a

Table 12. Key data on intestinal fluid parameters from animal models

A comparison of bile and phospholipid concentrations in the mid-jejunum of dogs and humans following a 500 mL meal of Ensure Plus ® was 18 mM and 11.8 mM for the bile and 19.4 mM and 4.31 mM for phospholipids [124].

4.5 Small intestinal pressures/motility

The MMC cycle in humans usually starts in the stomach but there are reports that the phase III contractions can start within the proximal small intestine [89]. The velocity of propagation of phase III of the MMC was reported to decrease progressively from the proximal duodenum to the distal jejunum from 11.4 ± 4.7 in the duodenum to 9.3 ± 5 at the junction of the duodenum and jejunum and 7.4 ± 5.8 cm min^{-1} in the jejunum (in humans) [89]. The duration of the phase III activity increased from the proximal duodenum to the distal jejunum from 5.4 ± 3 to 9.2 ± 9 minutes yet the frequency decreased from 11.7 ± 0.5 to 10.6 ± 1 [89]. The mean amplitude of a phase III contraction is 33 mg Hg in the duodenum in humans [90].

Motility within the small intestine of animals has been measured using a range of techniques including air-filled and water filled catheter systems in dogs [126]; telemetric capsules [43, 50]; ex vivo cannulated intestinal segments [127].

Propagation velocities of ileal contractions in dogs of 0.76 cm s^{-1} have been reported with the frequency of contractions being 17.8 contractions per minute [128].

The MMC is characterized by the regular reoccurrence of a period of irregular and low-amplitude contractions (Phase II) followed by a short period of intense burst of regular contractions (Phase III) propagating from the stomach or the duodenum to the ileum. MMC cycles occur approximately every 90 – 100 min in dogs [129] and humans, yet in rats it occurs at a much faster rate of 12 – 15 min [130]. In rat tissue, baseline small intestinal pressures of 4 mmHg have been reported where propulsive waves generated increased pressures of 9 mmHg that progressed at a velocity of 2 - 5 mm s^{-1} [127]. Pressures reported in the small intestine of dogs and pigs have included values of 100 - 300 mbar [50] and < 100 mbar [43] respectively.

The strength of small intestinal contractions in dogs measured using an ingested sensor reported maximum amplitude contractions ranging from 56 - 215mm Hg with a frequency of 0.5 contractions per minute [8]. A comparison of the crushing strength in the small intestine of dogs and humans showed that both revealed crushing strengths of 1.2 N which is lower than the gastric values for both species [131].

5 The Colon

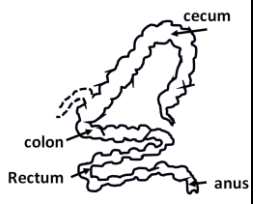
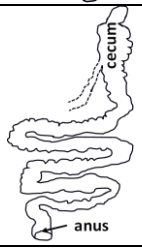
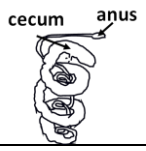
The human colon is the last site of absorption for undigested food. It is comprised of the caecum as well as ascending, transverse, descending and sigmoid colon and lastly, the rectum. The human colon has four bends. The first is located between the ascending and transverse sections (the so-called hepatic flexure), secondly between the transverse and descending colon (termed the splenic flexure) and the remaining two are found at the beginning and the end of the sigmoid colon.

The main functions of the colon are the absorption of water, electrolytes and nutrients from partially digested food as well as storage and distal propulsion of faecal matter until defecation. Every region of the human colon has a different role, e.g., right colon (i.e. caecum, ascending and mid-transverse absorbs more water and electrolytes than the left colon (i.e. descending, sigmoid and anal canal) [132].

5.1 Colon anatomy

The colon anatomy in humans and animals is compared in detail in Table 13. This includes details on the dimensions and arrangement of the colon as well as the fluid volumes and composition within the colon.

Species	Anatomy		
	Length (cm)	Diameter (cm)	Arrangement

	Cec	AC	TC	DC	SC	Cec	AC	TC	DC	SC	
Rats	0.9 - 1.1 [1] 5.46 ± 2.21 [133] [(3.8–7)^{4w}, (4–6.5)^{8w}, (3.5–8.5)^{38w}] [134]	$\begin{pmatrix} 4.98 \pm 1.0^{Prox.\ Col} \\ 8.93 \pm 1.76^{Dis.\ Col} \end{pmatrix}$ [133] [(11-15)^{4w}, (13-19)^{8w}, (16.5-21)^{38w}] [134]				2.08 ± 0.2 [133]	$\left(\begin{pmatrix} 0.82 \pm 0.03^{Macroscopic} \\ 0.93 \pm 0.04^{Radiological} \end{pmatrix}_{Prox.Col} \begin{pmatrix} 0.8 \pm 0.03^{Macroscopic} \\ 0.85 \pm 0.03^{Radiological} \end{pmatrix}_{Dis.Col} \right)$ [133]				
Mouse	3-4.4 [135][a] 3.5 ± 0.3 [136]	7.8 - 11.6 [135][a] 8.2 ± 0.5 [136]				5.4 ± 0.5 [136]	2.9 ± 0.1 [136]				
Rabbit	61 [1] 39 [42, 137] 41 [98]*	109 [42, 137] 83.16 [98]*				5.5 [98]*	3.4 [98]*				
Dog	0.8 [1]	5 [1]	7 [1]	12 [1]		1.9 [138]	2.8 [138]				
Monkey	(2-39)** [139]	(12-364)** [139]				(1.7-4.5) [140]	(1.7-4) [140]				
Pig	23 [1, 137]	750[1], 413 [42, 137]				3.0 [141]	(1.7 - 3.4) [141]				

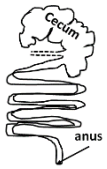
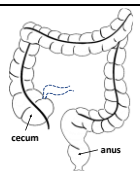
Guinea pig	15 [42, 137] (15 - 20) [23]	100 [42, 137]				(2.1 - 3.3) [1]	(0.14 - 0.5) [1]				
Human	6 [142]	16 ± 23.5 [143]	27.8 ± 5.4 [143]	23.7 ± 4.1 [143]	27.8 ± 11.2 [143]	1 – 3 [1]	[3.4-3.8] [143]	[3.3-3.5] [143]	[2.8-2.9] [143]		

Table 13 (continued)

Species	Anatomy	Physiology			
	Mucus (μm)	Fluid capacity (mL)	pH	Osmolality (mOsmol kg^{-1})	Buffer capacity (mmol l^{-1}ΔpH^{-1})
Rats	49.6 ± 31.5^{Cec} [144] 65.2 ±39.8 $^{Col\ asc}$ [144] 48.4 ±30 Col desc [144]	42[1]	$\begin{pmatrix}(6.2-6.4)_{cec}\\(6.2-6.4)_{Col}\end{pmatrix}_{fed}$ [42, 1 $\begin{pmatrix}\binom{(6.8-7.1)^{fasted}}{6.0^{fed}}_{Cec}\\\binom{6.8^{fasted}}{6.0^{fed}}_{Col}\end{pmatrix}$[145] [6^{cec}, 6.3$^{Prox.\ Col}$, (6.6^{f}/6.0^{m}) $^{Dis.\ col}$] fed [146]	(540^{Cec}, 545$^{Prox.\ Col}$)[123] [503^{Cec}, (420^{f}/508^{m})^{Col}]fed [146]	$\begin{pmatrix}\binom{(16.3-19.1)^{fasted}}{(19.5-34)^{fed}}_{Cec}\\\binom{(10-12)^{fasted}}{(22.4-24.8)^{fed}}_{Col}\end{pmatrix}$ [145] (39.4^{Cec}, 42.7$^{Prox.\ Col}$)[123] [(84^{f}/39.9^{m})^{Cec}, (78^{f}/44^{m})^{Col}]fed [146]
Mouse	n/a	$\binom{0.13\pm0.01^{Cec}}{2.9\pm0.1^{Col}}$ [136]	$(4.7^{fasted}, 4.5^{fed})$[147]	n/a	n/a
Rabbit	134.4 ± 88.4^{Cec}[144]	$\binom{353^{Cec}}{(117)^{Col}}$[148]	$\begin{pmatrix}(6.0-6.1)_{cec}\\(6.2-6.5)_{Col}\end{pmatrix}_{fed}$ [42, 1	466[149]	(34.2^{Cec}, 22.0$^{Prox.\ Col}$)[123]

	265.1 ± 125.6$^{Col\ asc}$[144] 63.2 ± 41.2$^{Col\ desc}$[144] 111.5 ± 99.6^{Rectum}[144]			(419^{Cec}, 372$^{Prox.\ Col}$)[123]	
Dog	n/a	$\left(\frac{(5-16)^{Cec}}{(20-90)^{Col}}\right)^{Car}$[148] $(200-300)^{Beagle}$[1]	$\left(\begin{pmatrix}(6.8-7.1)^{Cec}\\6.0^{Col}\end{pmatrix}_{Nrm}\ \begin{pmatrix}6.8^{Cec}\\6.0^{Col}\end{pmatrix}_{H-f}\right)_{fed}$[150]	n/a	n/a
Monkey	n/a	$\left(\frac{(1-955)^{Cec}}{(11-7800)^{Col}}\right)^{*}$[148]	(6.0_{cec}, 5.1_{col})	n/a	n/a
Pig	37.2 ± 16.1^{Cec}[144] 68.1 ± 36.5Col asc[144] 83.6 ± 36.2Col tran[144] 76.3 ± 56.7$^{Col\ desc}$[144] 58.8 ± 27.9^{Rectum}[144]	$\left(\frac{(10-902)^{Cec}}{(58-6042)^{Col}}\right)$[148]	$\left(\frac{6.1_{cec}}{(6.2-6.4)_{Col}}\right)_{fed}$[42, 137] (5.2-7.8)[43]	[(340-350)^{Cec}, (260-335)^{col}][151] 344 ±6.27$^{Prox.\ Col,\ fed}$ [152] (442^{Cec}, 470$^{Prox.\ Col}$, 496$^{Dis.\ Col}$)[123]	(41.5^{Cec}, 33.0$^{Prox.\ Col}$, 22.4$^{Dis.\ Col}$) [123]
Guinea pig	n/a	n/a	$\left(\frac{(6.2-6.4)_{cec}}{(6.1-6.4)_{Col}}\right)_{fed}$[42, 137]	n/a	n/a
Human	31.1^{Cec}[18] 34.4$^{Col\ asc}$[18] 50.5$^{Col\ tran}$[18] 62.0$^{Col\ desc}$[18]	(1000^{fasted} – 7000^{fed}) $^{Whole\ Col}$	(5.5 – 7.0)[1] [(5.5 – 6.5)^{Cec}, (5.5–7.5)$^{Col\ asc.}$ 7.0 – 8.0$^{Col\ desc.}$][147]	(224 ± 125^{fed}, 81 ± 102^{fasted}) $^{Col\ asc.\ -Healthy}$ [153], (144 - 267) $^{Cec-healthy}$ [154], (199.6 - 290) $^{UC-Col\ asc.\ fasted}$ [155]	18.9$^{Prox.\ Col}$ [153] 44.4$^{Dis.\ Col}$ [156]

n/a: not available; a Length depends on animal's weight[135]; b depending on gender with not significant difference between fasted and fed state in Wistar rats [145]; Cec: cecum; AC: Ascending; TC: Transverse; DC: Descending; SC: Sigmoid Colon; Col: colon; Col asc.: colon ascending; Col desc.: colon descending; UC: Ulcerative Colitis; Prox. Col: proximal colon; Dis. Col: distal colon; *White New Zealand Rabbit (Oryctolagus cuniculus); **for species-dependent lengths of cecum and colon see McGrosky et al 2019 [139]; ***the anatomical volume depends on the species and the authors will like to refer to Chivers and Hladik 1980 [148] for all the monkeys species(Old and New world) individual anatomical volumes; Nrm: normal diet of dogs (125g lean meat, 100g cracker meal, 15g lard, 30g bone ash and 300 mL water) [150]; H-f: high fat diet of dogs (50g meat, 50g cracker meak, 180g, 180g lard and 30g bone ash) [150]; f: female; m: male; 3w, 8w and 38w reflects the age of Wistar rats (i.e. 3 weeks, 8 weeks and 38 weeks) used in Merchant et al study [134]

Table 13. Comparison of anatomical and physiological aspects of the colon of humans and animal models

The colons of rabbits and pigs share anatomical similarities with the human colon, in terms of haustra and semilunar folds, making these two species suitable to explore transit times in the colon [1, 157]. However, there are still significant interspecies differences, e.g., pigs and humans, as pigs' colon constitutes a spiral arrangement and possesses a much larger cecum [157].

5.2 Colonic pressure/motility

Recent studies have used telemetric technology to obtain dynamic pH and pressure profiles in animals [43, 50]. Aside from the anatomical similarities, pigs showed higher pressure amplitudes in fasted (Figure 4A) and fed (Figure 4B) state compared to humans. On the other hand, dogs showed close to human pressure profiles with low variability; probably this can be attributed to the short colon in dogs. It should be pointed out that the direct comparison of animals and humans should be performed with caution as the location of the SmartPill® capsule is unknown and hence the pressure and pH registration cannot be linked to a specific colonic region [70]. Although this technology provides information for the luminal environment of the whole colon, the colonic regional residence times are not known in order to understand for how long a dosage form or device will be exposed under specific conditions. For instance, studies using the magnetic pill as tracker of colonic motility in healthy humans showed longer transit times in the proximal part of the colon (ascending and transverse) compared to the distal part [158]. If this is the case for animals (there are no animal studies using magnetic capsule), then it is important to know the location of the wireless pH/pressure sensor to inform fields such as formulation development.

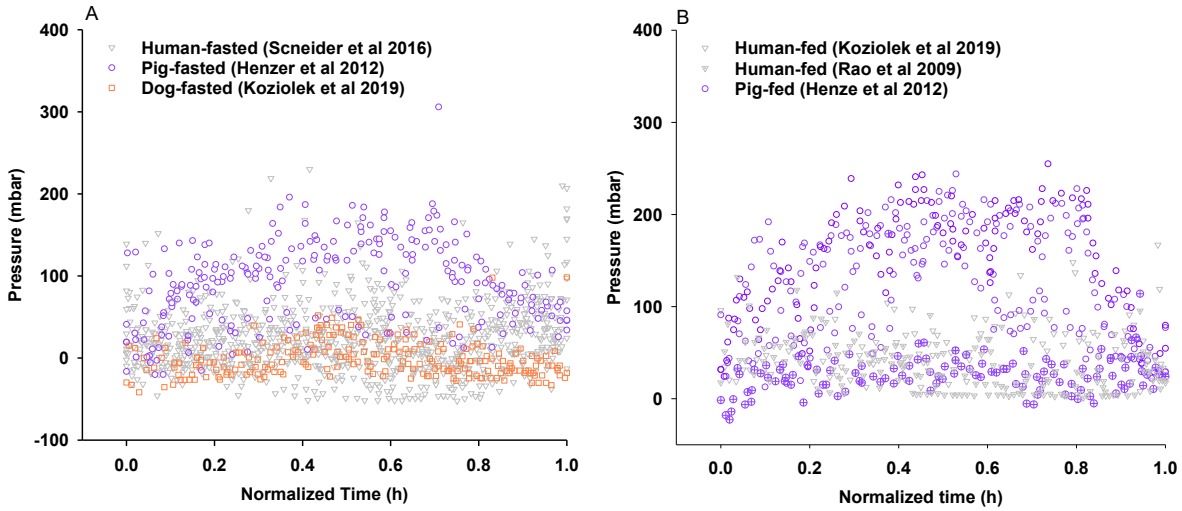


Figure 4. Pressure profiles of the whole colon in humans (n=10) using Intellicap® [100], pigs (n=4) [43] and dogs (n=6) [50]using SmartPill® under fasted (A) and fed (B) conditions. In fed state only one pig (⊕) in the Henze et al study (n=4) showed a pressure profile within the range observed in the corresponding human studies.

Pigs have shown a "parabolic" pressure profile (Figure 4) compared to the highly variable but fairly constant range of pressures across the human colon. In the human colon, pressure ranges between 1.1 and 231 mbar in fasted and 0.55 - 168 mbar in fed state. In the dog colon, pressure ranges

between 0.5 and 98 mbar in fasted state. The pressure amplitudes in the pig colon range between 2.1 and 305 and 1 – 256 mbar in the fasted and fed state respectively. Thus, a dosage form targeting the colon will be exposed to a significantly heterogeneous environment in the pig colon, unless it spends most of the time within the proximal part in which the pressure amplitudes have the same range as humans (see data points for the pig that are lying within the first 0 - 0.1 normalised time (h) in Figure 4, these show similarity to those in humans and dogs). However, this is more of a speculation rather than a solid assumption as knowledge of regional pressure amplitudes is required.

5.3 Colonic pH

With regards to pH profile, pigs showed high variability with values between pH 5.5 and pH 10 in fasted (Figure 5A) and 5.4 to 8.2 in fed (Figure 5B) state. Interestingly, pig colonic pH profile was highly variable in fasted but not that in fed which was exactly the opposite for humans. Dogs showed pH values between 5 and 8.3 in fasted state (Figure 5A). In addition, dogs showed constant pH for relatively long periods which has not been observed in a distinctive manner in humans and pigs. This is probably related to the shorter canine colon, implying that the SmartPill® might have passed from the proximal colon to the rectum in quite a short time and remained there until defecation [50]. This might also explain the relatively low variability in the observed pressure profiles (Figure 4A).

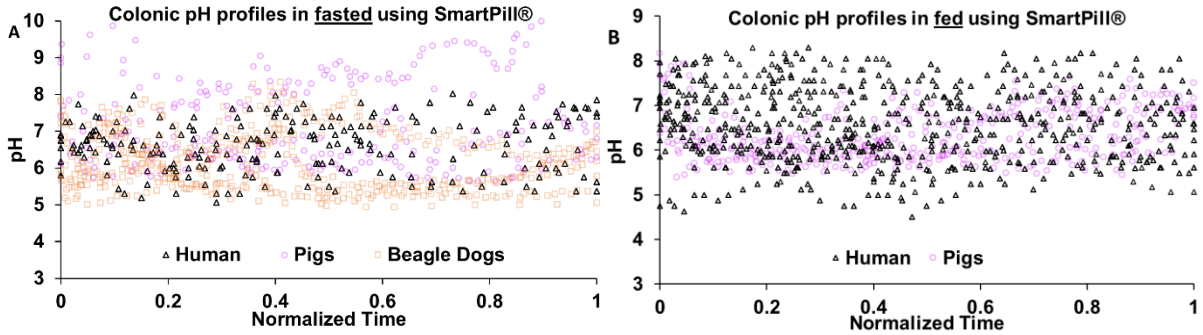


Figure 5. pH profiles of the whole colon in human (n=10) using Intellicap® [100], pigs (n=4) [43] and dogs (n=6) [50] using SmartPill® under fasted (A) and fed (B) conditions.

These recent studies revealed an important gap on how the characterization of the GI tract in preclinical species has been translated/extrapolated to humans and/or used to develop in vitro models and that a single attribute (e.g., anatomy or a single value of luminal pH) is not enough to assess the suitability of an animal.

Saying this, an urgent area is the development of suitable wireless technologies to expand the dynamic characterization of the colon in small animal models (i.e., rats, mouse and guinea pig). This will allow to withdraw conclusions for the suitability of the small animals and potentially to redesign e.g., the simulation of the media to properly reflect physiological conditions.

Beside any fundamental difference in physiology and anatomy between animal models and humans, a harmonization of the study protocols in terms of caloric intake, volume, viscosity should also be considered.

The differences in pH and pressure amplitudes between animals and humans as well as between the two states for each species, are related to the underlying regional secretions, absorption rates, microbiota and more importantly to motility patterns.

Clinical studies increasingly require adequate animal models to develop and assess new therapies. Thus, changes in colonic motility of animals under different large bowel disorders should be equivalent to humans. However, this requires a rational use of terminology to describe those motility patterns that are equivalent to those observed in humans. Recently, there is an effort to harmonize the terminology. Direct comparison of the colonic motility patterns between human and animals is not easy.

5.4 Evaluation of Colon Transit in Humans and Animals

A comparison of colonic transit in humans and animals is presented in Table 14.

5.4.1 Radiopaque Markers

Radiopaque markers (RMs) have been used to measure segmental and total colonic transit times. Different approaches to measure colonic transit with RMs have been described elsewhere [159-162]. The minimum number of markers required to be ingested daily should be at least 10 – 12 for reporting reasonably accurate colonic transit time in days or hours [163].

Depending on the distribution of markers, normal and abnormal functionality of the regions of the colon can be assessed. For instance, accumulation of markers in the rectosigmoid area might imply functional outlet obstruction, whilst distribution along the region suggests slow-transit constipation. However, this is not a diagnostic method because delayed rectosigmoid transit resulting from pelvic floor dyssynergia may inhibit proximal colonic transit and result in widespread distribution of markers.

The radiopaque marker is a well-established method, and it is readily available and reasonably inexpensive. RMs are the reference standard for the evaluation of colonic transit times in clinical practice [164].

5.4.2 Colonic Scintigraphy

Scintigraphy (SC) is a relatively safe, non-invasive method and correlates with RMs. SC provides kinetics of ascending colon (AC) emptying and total colon transit [165]. The most common method is for subjects to ingest a pH-sensitive coated capsule containing indium-111–labeled activated charcoal particles after fasting overnight. The coated capsule dissolves in the terminal ileum and releases the radiolabelled tracer into the lumen [166]. Alternatively, a whole-gut transit test, including colonic transit, can be performed using a radiolabeled solid–liquid meal [167]. Then, repeated images of 2 min duration are acquired with a gamma camera at several time intervals after meal ingestion to appraise colonic transit [168]. The data is presented as a geometric mean (weighted average) of radioactivity based either on 5 [168] or 7 regions [167]. The recording times required to fully assess functionality of the colon are at 24, 48, and 72 hours.

Application of SC in patients with diarrhoea or constipation, normal values, coefficients of variation performance characteristics and differences between slow colonic transit constipation and

defecation disorders as well as relationship between colonic transit summaries of prolonged recordings and bowel function symptoms have been well documented [169-172].

High intraindividual coefficients of variation has been observed between different measuring times, e.g., 31 % at 24 hours vs 27 % at 48 hours over a period of less than 3 weeks, and 38 % at 24 hours vs 30% at 48 hours over a median interval of 2 years [169]. This variation reflects the underlying physiological, natural variation in colonic motility, stool frequency and consistency.

In several diseases, like functional diarrhoea, carcinoid diarrhoea, irritable bowel syndrome and idiopathic constipation, the whole colonic SC transit and ascending colon (AC) emptying have been reported to be abnormal [173, 174]. Thus, colon motility might serve as biomarker of colonic function in diseases and as a surrogate end point in the evaluation of drug therapy [175].

5.4.3 Use of Wireless pH capsule to Measure Colonic Transit

The arrival of the wireless motility capsule (WMC) into the cecum is determined by a sharp decrease of pH which is more than one unit and lasts for at least 5 minutes; with this method, the colonic transit time is defined as the time from entry into the cecum to the time the WMC passes out of the colon with the sudden loss of pressure recordings and a decrease in temperature. The colonic transit time measured in 87 healthy and 78 constipated subjects showed a median value of 21.7 h (IQR, 15.5–37.3 h; 95th percentile, 59 h) in healthy subjects and 46.7 h (IQR, 24.0 – 91.9 h) in constipated patients [176]. A significant correlation between the WMC and the percentage of radiopaque markers retained on fifth day was found (r = 0.69) in constipated patients studied simultaneously with both methods [176].

High agreement of 87 % for classifying subjects as having slow or normal colonic transit was found in a large multicenter study of 158 patients with constipation, using WMC method [177]. Moreover, characterization of colonic pressure activity in healthy controls and in constipated patients has been performed using WMC technology [178].

The advantages of the WMC to assess colonic transit times over the previous techniques are no radiation exposure, its non-invasive nature and allowing for whole gut and regional transit. However, distinguishing the entry into the cecum by the pH drop, is sometimes difficult. Moreover, the method is more expensive than other methods, like RMs and SC, to measure colonic or whole-gut transit. Moreover, this method does not provide information about the location of the capsule within the different regions of the small intestine and the colon.

5.4.4 Use of (electro)magnetic capsules to measure colonic transit

The use of electromagnetic capsules, like the electromagnetic Motilis 3D-Transit system, to measure colonic transit has been reviewed elsewhere [179]. The advantage of this method is the spatiotemporal resolution that allows assessment of regional colonic transit times which is not possible with other ambulatory methods, such as the wireless motility capsule. Although this technology has been used in several human studies, including patients, animal studies are needed to provide information about the regional and total colonic transit times to allow comparison between different species.

The first feasibility study using a magnetic capsule was conducted by Stathopoulos et al [180] in healthy subjects. The authors showed that it was possible to obtain a 3D configuration of the GI tract as well as dynamic measurements of the internal gut environment via magnet displacements, such as velocity and transit times. Few years later Worsøe et al [181] validated the technology against

PillCam. The authors demonstrated that it could distinguish the between the contraction frequencies of the small intestine in the fasted and fed state.

Further improvements are required to make this technology suitable for commercial use and to decrease the data losses during recording. The latter occurring due to loss of transmission signal and poor recording quality.

Colonic Transit times (h)											
Status	Region	Method	Rats	Mice	Rabbits	Dogs	Pig		Monkey	Human	
							Adult	Mini pig		m	f
Fasted	Colon	Radio-opaque				28.4 [182]		6 – 54.5 [a][183]		34.7 30.7 ± 3 [161]	38.8 ± 2.9 [161]
								9.5 – 30.5 [b][183]		32.6 ± 7.7 [184]	34.5 ± 5.87 [184]
								25 – 54.5 [c][183]			
								12 – 53.5 [d][183]		7.4 ± 9.3 [185]	25.8 ± 24.1 [185]
								7 [e][183]		45.6 ± 22.7 [186]	
										34.7 ± 17.4 [187]	
		SmartPill®				25.4 ± 3.3 [50]	53.77 ± 31.7 [Landrace][43]			12.4 ± 8.7 [188]	
		Magnetic Pill/capsule									24.3 [189]
		MRI								31 ± 10[190]	41 ± 9 [190]
										30.9 ± 15.9 [187]	
	Left-Colon	Radio-opaque								8.7 ± 1.5 [161]	13.7 2.1 [161]
										7.8 ± 2.8 [184]	8.6 ± 2.9 [184]
										0.9 ± 2.0 [185]	1.3 ± 3.1 [185]
										3.2 ± 11.3 [186]	

	Rectosigmoid									13 ± 1.7 [161]	11.8 ± 1.6 [161]
										5.4 ± 2.3 [184]	5.0 ± 2.2 [184]
										4.4 ± 7.1 [185]	14 ± 13.8 [185]
										13.1 ± 5.1 [186]	
	Right-Colon									8.9 ± 1.1 [161]	13.3 ± 1.6 [161]
										3.4 ± 5.7 [185]	10.1 ± 12.7 [185]
										19.2 ± 11.1 [186]	
										19.5 ± 4.4 [184]	20.8 ± 4.6 [184]
Fed	Asc. Colon	Radio-opaque								9.9 ± 3.8 [165]	
		Magnetic Pill								5.3 ±2.4 [158]	
		^{11}In-Pellets								11.9 ± 7.48 [165]	
	Cec-Asc colon	Magnetic Pill								5.3 ± 6.97 [191]	
	Colon	Radio-opaque								24.5 ± 18.8 [192]	
										39.2 [193]	
										30.7 ± 17.5 [161]	38.8 ± 18.1 [161]
										25.6 ± 16.9† [194]	38.9 ± 16.9† [194]
										26.2 ± 8.3 [165]	
										34.7 ± 26.6 [195]	
		Combination of Colored plastic beads and Sulfasalazine (pro-drug)				39.4 ± $1.6_{G.S}$ [196]					
						29.3 ± $1.3_{G.D}$ [196]					
						9.1 ± $1.1_{M.P}$ [196]					
						18.5 ± $3_{S.S}$ [196]					

		SmartPill®				28.2 ±4.7[50] Beagle	102.5 ±59.54[43] Landrace			15.6 ±12.23[100]	
										19.6 ±10.4[176]	28.4 ±19.9[176]
										20.17 ±14.56 (2.62 – 67.15)[109]	
										14.9 ±11.5[188]	
		Magnetic Pill/capsule									19.96 ±11.95 (1.5 – 43.7)[197]
											26 ±11.4 (8.7 – 63.5)[197]
											19.36 ±9.2 (4.6 – 41.8)[197]
										18.2 (1.5 – 43.7)[198]	
										21.2 ±3.9[158]	
										20 ±8.9[191]	
		Solid Marker			9.5 ±0.5[199]						
		^{11}In-Pellets								35.7 ±22.45[165]	
		Pellets	5.6$_{H-S}$[86]								
			5.8$_{L-S}$[86]								
			8.8$_{L-B}$[86]								
	Descending colon	Magnetic Pill								1.1 ±1.55[191]	
										1.9 ±1.4[158]	
	Left-Colon	Radio-opaque								9.5 ±10.8[192]	
										12.7[193]	
										8.7 ±8.7[161]	13.7 ±13.1[161]

										7.1 ±7.5†[194]	14.2± 12.1†[194]
										9.1 ±8.5[195]	
	Middle /Distal Colon	Magnetic Pill								14.2 (0.3 – 41.9)[198]	
	Proximal Colon	Radio-opaque			60.4 ±19.8 h.f[200]						
					47.1 ±12.2 h.f[200]						
					36.3 ±9.7 h.f [200]						
					25 ±12.5 s.f[200]						
					28.6 ±11.5 s.f[200]						
					24 ±16.8 s.f[200]						
		Magnetic Pill/capsule								2.1 (0.0 – 22.1)[198]	
		Dye Marker					94.8 ±59.9[152]				
	RectoSigmoid	Radio-opaque								9.2 ±11.4[192]	
										11.5[193]	
										13 ±9.9[161]	11.8 ±10.0[161]
										8.2 ±8.4[194]	11.5 ±11.1[194]
		Magnetic Pill								6.7 ±7.66[191]	
										2.8 ±3.2[158]	
	Right-Colon	Radio-opaque								5.8 ±5.3[192]	
										7.9[193]	
										8.9 ±6.4[161]	13.3 ±10[161]
										10.2 ±9.1[194]	13.1 ±9.4[194]
										12.3 ±12.4[195]	

	Transverse colon	Magnetic Pill								4.7 ±4.64[191]
										4.9 ±2.0[158]

Footnotes: [a]3 days postweaning piglets. 25 – 40% of the pellets presented in Cecum[183]; [b]sucking piglets. 50 – 75% of the pellets presented in Colon[183]; [c]3 days postweaning piglets. 30 – 50% of the pellets presented in Colon[183]; [d]2 weeks postweaning piglets. 30 – 50% of the pellets presented in Colon[183]; [e]3 weeks postweaning piglets. 30 – 50% of the pellets presented in Colon[183]; [f]The data reported as median and 95%CI range[158]; [g]There is a statistically significant difference (p<0.001) between male (n=77) and female (n=57)[194]; [h] Silver metal radiopaque markers was injected in the proximal colon of male Sprague-Dawley rats; [i]Winnie mouse[201]; [j] Trypan blue was injected in the proximal colon of male Sprague-Dawley rats[202]; Giant Schnauzer (G.S), Great Dane (G.D), Miniature Poodle (M.P), Standard Schnauzer (S.S)[196]; **H**igh density, 1.5 g cm^{-3}, and **S**mall diameter 1 mm (H-S) pellets, **L**ow density, 0.9 g cm^{-3}, and **S**mall diameter 1 mm (L-S) pellets and **L**ow density, 0.9 g cm^{-3}, and **B**ig diameter 1.25-1.60 mm (L-B) pellets[86]; hard faeces (h.f) and soft faeces (s.f)[200]

Table 14. Comparison of colonic transit times between human and animal models

6 Conclusions

An extensive review on animals and human physiology and the methods used to analysis different parameters was performed. There are considerable anatomical, physiological and pathophysiological differences between animal models and human. Thus, there is no single, "gold-standard" animal model that can reproduce all the aspects and be used to extrapolate findings to human physiology. In addition, the analytical/monitoring method used to obtain information about GI tract environment, further complicating the extrapolation from animal to humans. However, significant improvements in tracking systems have permitted increased understanding of human GI tract environment. Nevertheless, the animal studies are limited, especially in small animals due to incompatibility issues, e.g., size of capsules. There is a catch 22 whereby small ingestible devices are required to characterise the GI environment in small animals that can subsequently permit evaluation of newer devices.

In terms of the most suitable animal model to use to evaluate an ingested device, this still relates to the primary function of the device under test to ensure that the study aims are met. However, it is important to recognise limitations in certain animal models for certain aspects of GI environment and their ability to replicate the human.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

COF received funding from the EPSRC Centre for Doctoral Training in Formulation Engineering (EP/L015153/1) and AstraZeneca AB R&D, Gothenburg.

References

[1] T.T. Kararli, Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals, Biopharm Drug Dispos, 16 (1995) 351-380.
[2] K. Vdoviaková, E. Petrovová, M. Maloveská, L. Krešáková, J. Teleky, M.Z.J. Elias, D. Petrášová, Surgical Anatomy of the Gastrointestinal Tract and Its Vasculature in the Laboratory Rat, Gastroenterology Research and Practice, 2016 (2016) 2632368.
[3] C. Van de Bruaene, D. De Looze, P. Hindryckx, Small bowel capsule endoscopy: Where are we after almost 15 years of use?, World J Gastrointest Endosc, 7 (2015) 13-36.
[4] M. Camilleri, D.R. Linden, Measurement of Gastrointestinal and Colonic Motor Functions in Humans and Animals, Cellular and Molecular Gastroenterology and Hepatology, 2 (2016) 412-428.
[5] M. Appleyard, Z. Fireman, A. Glukhovsky, H. Jacob, R. Shreiver, S. Kadirkamanathan, A. Lavy, S. Lewkowicz, E. Scapa, R. Shofti, P. Swain, A. Zaretsky, A randomized trial comparing wireless capsule endoscopy with push enteroscopy for the detection of small-bowel lesions, Gastroenterology, 119 (2000) 1431-1438.
[6] C.S. Boillat, F.P. Gaschen, G.L. Hosgood, Assessment of the relationship between body weight and gastrointestinal transit times measured by use of a wireless motility capsule system in dogs, Am J Vet Res, 71 (2010) 898-902.
[7] C.S. Boillat, F.P. Gaschen, L. Gaschen, R.W. Stout, G.L. Hosgood, Variability associated with repeated measurements of gastrointestinal tract motility in dogs obtained by use of a wireless motility capsule system and scintigraphy, Am J Vet Res, 71 (2010) 903-908.
[8] P. Boscan, S. Cochran, E. Monnet, C. Webb, D. Twedt, Effect of prolonged general anesthesia with sevoflurane and laparoscopic surgery on gastric and small bowel propulsive motility and pH in dogs, Vet Anaesth Analg, 41 (2014) 73-81.
[9] J. Kvetina, M. Kunes, J. Bures, M. Kopacova, I. Tachecí, S. Spelda, V. Herout, S. Rejchrt, The use of wireless capsule enteroscopy in a preclinical study: a novel diagnostic tool for indomethacin-induced gastrointestinal injury in experimental pigs, Neuro Endocrinol Lett, 29 (2008) 763-769.
[10] Q. Shi, J. Wang, D. Chen, J. Chen, J. Li, K. Bao, In Vitro and In Vivo characterization of wireless and passive micro system enabling gastrointestinal pressure monitoring, Biomedical Microdevices, 16 (2014) 859-868.
[11] A.M. Stokes, N.L. Lavie, M.L. Keowen, L. Gaschen, F.P. Gaschen, D. Barthel, F.M. Andrews, Evaluation of a wireless ambulatory capsule (SmartPill®) to measure gastrointestinal tract pH, luminal pressure and temperature, and transit time in ponies, Equine Vet J, 44 (2012) 482-486.
[12] C. O'Farrell, K. Stamatopolous, M.J.H. Simmons, H.K. Batchelor, In vitro models to evaluate ingestible devices: present status and current trends, Advanced Drug Delivery Reviews, Submitted (2021).
[13] I.A. El-Sayes, T.N. Abdelbaki, M.A. Sharaan, M.S. Shaaban, M.M. El Shafei, M.R. Elkeleny, Sleeve Volume and Preoperative Gastric Volume Assessment Using Three-dimensional MDCT Gastrography and Their Correlation to Short-term Post-Sleeve Gastrectomy Weight Loss, Obesity Surgery, 31 (2021) 490-498.
[14] A. Csendes, A.M. Burgos, Size, Volume and Weight of the Stomach in Patients with Morbid Obesity Compared to Controls, Obesity Surgery, 15 (2005) 1133-1136.
[15] S.H. Kim, B. Keum, H.S. Choi, E.S. Kim, Y.S. Seo, Y.T. Jeen, H.S. Lee, H.J. Chun, S.H. Um, C.D. Kim, Stomach Volume Assessment Using Three-dimensional Computed Tomography Gastrography for Bariatric Treatment, Obesity Surgery, 30 (2020) 401-406.
[16] A. Geliebter, Gastric distension and gastric capacity in relation to food intake in humans, Physiology & Behavior, 44 (1988) 665-668.
[17] T.T. Kararli, Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals, Biopharmaceutics & Drug Disposition, 16 (1995) 351-380.

[18] G.B. Hatton, V. Yadav, A.W. Basit, H.A. Merchant, Animal Farm: Considerations in Animal Gastrointestinal Physiology and Relevance to Drug Delivery in Humans, Journal of Pharmaceutical Sciences, 104 (2015) 2747-2776.
[19] C. Wang, B. Zhai, H. Guo, P. Wang, Z. Liu, H. Gu, H. Ho, P. Langguth, K. Li, C. Wang, Z. Hao, In vivo measurement of gastric fluid volume in anesthetized dogs, Journal of Drug Delivery Science and Technology, 55 (2020) 101488.
[20] S.-F. Jang, B.A. Goins, W.T. Phillips, C. Santoyo, A. Rice-Ficht, J.T. McConville, Size discrimination in rat and mouse gastric emptying, Biopharmaceutics & Drug Disposition, 34 (2013) 107-124.
[21] M.N. Martinez, J.P. Mochel, S. Neuhoff, D. Pade, Comparison of Canine and Human Physiological Factors: Understanding Interspecies Differences that Impact Drug Pharmacokinetics, The AAPS journal, 23 (2021) 59.
[22] H. Guo, C. Wang, Z. Liu, H. Gu, Y. Li, L. Zhao, R. Hou, J. Zhu, H. Ho, Z. Hao, Quantification of in vivo gastric fluid volume in Bama miniature pigs in fasted state, 39 (2018) 403-407.
[23] A. Goyanes, G.B. Hatton, A.W. Basit, A dynamic in vitro model to evaluate the intestinal release behaviour of modified-release corticosteroid products, Journal of Drug Delivery Science and Technology, 25 (2015) 36-42.
[24] D. Armstrong, Review article: gastric pH -- the most relevant predictor of benefit in reflux disease?, Alimentary pharmacology & therapeutics, 20 Suppl 5 (2004) 19-26; discussion 38-19.
[25] H.P. Simonian, L. Vo, S. Doma, R.S. Fisher, H.P.J.D.d. Parkman, sciences, Regional postprandial differences in pH within the stomach and gastroesophageal junction, 50 (2005) 2276-2285.
[26] A. Lindahl, A.-L. Ungell, L. Knutson, H. Lennernäs, Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women, Pharmaceutical Research, 14 (1997) 497-502.
[27] G. McLauchlan, G. Fullarton, G. Crean, K.J.G. McColl, Comparison of gastric body and antral pH: a 24 hour ambulatory study in healthy volunteers, 30 (1989) 573-578.
[28] W.J. Fan, Y.T. Hou, X.H. Sun, X.Q. Li, Z.F. Wang, M. Guo, L.M. Zhu, N. Wang, K. Yu, J.N. Li, M.Y. Ke, X.C. Fang, Effect of high-fat, standard, and functional food meals on esophageal and gastric pH in patients with gastroesophageal reflux disease and healthy subjects, 19 (2018) 664-673.
[29] M. Koziolek, M. Grimm, D. Becker, V. Iordanov, H. Zou, J. Shimizu, C. Wanke, G. Garbacz, W.J.J.o.p.s. Weitschies, Investigation of pH and temperature profiles in the GI tract of fasted human subjects using the Intellicap® system, 104 (2015) 2855-2863.
[30] J.B. Dressman, R.R. Berardi, L.C. Dermentzoglou, T.L. Russell, S.P. Schmaltz, J.L. Barnett, K.M.J.P.r. Jarvenpaa, Upper gastrointestinal (GI) pH in young, healthy men and women, 7 (1990) 756-761.
[31] T.L. Russell, R.R. Berardi, J.L. Barnett, L.C. Dermentzoglou, K.M. Jarvenpaa, S.P. Schmaltz, J.B.J.P.r. Dressman, Upper gastrointestinal pH in seventy-nine healthy, elderly, North American men and women, 10 (1993) 187-196.
[32] P.-J. Lu, P.-I. Hsu, C.-H. Chen, M. Hsiao, W.-C. Chang, H.-H. Tseng, K.-H. Lin, S.-K. Chuah, H.-C.J.W.j.o.g.W. Chen, Gastric juice acidity in upper gastrointestinal diseases, 16 (2010) 5496.
[33] V. Savarino, G.S. Mela, P. Scalabrini, A. Sumberaz, G. Fera, G.J.D.d. Celle, sciences, 24-hour study of intragastric acidity in duodenal ulcer patients and normal subjects using continuous intraluminal pH-metry, 33 (1988) 1077-1080.
[34] A. Press, I. Hauptmann, L. Hauptmann, B. Fuchs, M. Fuchs, K. Ewe, G.J.A.p. Ramadori, therapeutics, Gastrointestinal pH profiles in patients with inflammatory bowel disease, 12 (1998) 673-678.
[35] J. Fallingborg, L. Christensen, M. Ingeman-Nielsen, B. Jacobsen, K. Abildgaard, H.J.A.p. Rasmussen, therapeutics, pH-profile and regional transit times of the normal gut measured by a radiotelemetry device, 3 (1989) 605-614.
[36] Y. Sasaki, R. Hada, H. Nakajima, S. Fukuda, A.J.A.J.o.G. Munakata, Improved localizing method of radiopill in measurement of entire gastrointestinal pH profiles: colonic luminal pH in normal subjects and patients with Crohn's disease, 92 (1997).

[37] V.C. Ibekwe, H.M. Fadda, E.L. McConnell, M.K. Khela, D.F. Evans, A.W.J.P.r. Basit, Interplay between intestinal pH, transit time and feed status on the in vivo performance of pH responsive ileo-colonic release systems, 25 (2008) 1828-1835.
[38] A. Lydon, C. Murray, J. McGinley, R. Plant, F. Duggan, G.J.C.J.o.A. Shorten, Cisapride does not alter gastric volume or pH in patients undergoing ambulatory surgery, 46 (1999) 1181.
[39] L. Kalantzi, K. Goumas, V. Kalioras, B. Abrahamsson, J.B. Dressman, C.J.P.r. Reppas, Characterization of the human upper gastrointestinal contents under conditions simulating bioavailability/bioequivalence studies, 23 (2006) 165-176.
[40] A.Y. Abuhelwa, D.J.R. Foster, R.N. Upton, A Quantitative Review and Meta-Models of the Variability and Factors Affecting Oral Drug Absorption-Part I: Gastrointestinal pH, The AAPS journal, 18 (2016) 1309-1321.
[41] E.L. McConnell, A.W. Basit, S. Murdan, Measurements of rat and mouse gastrointestinal pH, fluid and lymphoid tissue, and implications for in-vivo experiments, Journal of Pharmacy and Pharmacology, 60 (2008) 63-70.
[42] H.A. Merchant, E.L. McConnell, F. Liu, C. Ramaswamy, R.P. Kulkarni, A.W. Basit, S. Murdan, Assessment of gastrointestinal pH, fluid and lymphoid tissue in the guinea pig, rabbit and pig, and implications for their use in drug development, European Journal of Pharmaceutical Sciences, 42 (2011) 3-10.
[43] L.J. Henze, N.J. Koehl, H. Bennett-Lenane, R. Holm, M. Grimm, F. Schneider, W. Weitschies, M. Koziolek, B.T. Griffin, Characterization of gastrointestinal transit and luminal conditions in pigs using a telemetric motility capsule, European Journal of Pharmaceutical Sciences, 156 (2021) 105627.
[44] M. Hossain, W. Abramowitz, B.J. Watrous, G.J. Szpunar, J.W. Ayres, Gastrointestinal transit of nondisintegrating, nonerodible oral dosage forms in pigs, Pharmaceutical research, 7 (1990) 1163-1166.
[45] P. Mojaverian, Evaluation of gastrointestinal pH and gastric residence time via the Heidelberg Radiotelemetry Capsule: Pharmaceutical application, Drug Development Research, 38 (1996) 73-85.
[46] K.M. Mahar, S. Portelli, R. Coatney, E.P. Chen, Gastric pH and Gastric Residence Time in Fasted and Fed Conscious Beagle Dogs using the Bravo® pH System, Journal of Pharmaceutical Sciences, 101 (2012) 2439-2448.
[47] K. Sagawa, F. Li, R. Liese, S.C. Sutton, Fed and fasted gastric pH and gastric residence time in conscious beagle dogs, J Pharm Sci, 98 (2009) 2494-2500.
[48] M. Akimoto, N. Nagahata, A. Furuya, K. Fukushima, S. Higuchi, T. Suwa, Gastric pH profiles of beagle dogs and their use as an alternative to human testing, European Journal of Pharmaceutics and Biopharmaceutics, 49 (2000) 99-102.
[49] E.P. Chen, K.M.M. Doan, S. Portelli, R. Coatney, V. Vaden, W. Shi, Gastric pH and gastric residence time in fasted and fed conscious cynomolgus monkeys using the Bravo® pH system, Pharmaceutical research, 25 (2008) 123-134.
[50] M. Koziolek, M. Grimm, T. Bollmann, K.J. Schäfer, S.M. Blattner, R. Lotz, G. Boeck, W. Weitschies, Characterization of the GI transit conditions in Beagle dogs with a telemetric motility capsule, European Journal of Pharmaceutics and Biopharmaceutics, 136 (2019) 221-230.
[51] M. Koziolek, M. Grimm, G. Garbacz, J.-P. Kühn, W. Weitschies, Intragastric Volume Changes after Intake of a High-Caloric, High-Fat Standard Breakfast in Healthy Human Subjects Investigated by MRI, Molecular Pharmaceutics, 11 (2014) 1632-1639.
[52] N. Ramsbottom, M.T. Knox, J.N. Hunt, Gastric emptying of barium sulphate suspension compared with that of water, 18 (1977) 541-542.
[53] D.N. Bateman, T.A. Whittingham, Measurement of gastric emptying by real-time ultrasound, 23 (1982) 524-527.
[54] W. Schwizer, H. Maecke, F. Michael, Measurement of gastric emptying by magnetic resonance imaging in humans, Gastroenterology, 103 (1992) 369-376.
[55] D.M. Mudie, K. Murray, C.L. Hoad, S.E. Pritchard, M.C. Garnett, G.L. Amidon, P.A. Gowland, R.C. Spiller, G.E. Amidon, L. Marciani, Quantification of Gastrointestinal Liquid Volumes and Distribution

Following a 240 mL Dose of Water in the Fasted State, Molecular Pharmaceutics, 11 (2014) 3039-3047.
[56] M. Grimm, E. Scholz, M. Koziolek, J.P. Kühn, W. Weitschies, Gastric Water Emptying under Fed State Clinical Trial Conditions Is as Fast as under Fasted Conditions, Mol Pharm, 14 (2017) 4262-4271.
[57] M. Grimm, M. Koziolek, M. Saleh, F. Schneider, G. Garbacz, J.P. Kühn, W. Weitschies, Gastric Emptying and Small Bowel Water Content after Administration of Grapefruit Juice Compared to Water and Isocaloric Solutions of Glucose and Fructose: A Four-Way Crossover MRI Pilot Study in Healthy Subjects, Molecular Pharmaceutics, 15 (2018) 548-559.
[58] L. Marciani, P.A. Gowland, R.C. Spiller, P. Manoj, R.J. Moore, P. Young, A.J. Fillery-Travis, Effect of meal viscosity and nutrients on satiety, intragastric dilution, and emptying assessed by MRI, 280 (2001) G1227-G1233.
[59] N. Goelen, J. de Hoon, J.F. Morales, C. Varon, S. Van Huffel, P. Augustijns, R. Mols, M. Herbots, K. Verbeke, T. Vanuytsel, J. Tack, P. Janssen, Codeine delays gastric emptying through inhibition of gastric motility as assessed with a novel diagnostic intragastric balloon catheter, Neurogastroenterology & Motility, 32 (2020) e13733.
[60] A.Y. Abuhelwa, D.J.R. Foster, R.N. Upton, A Quantitative Review and Meta-models of the Variability and Factors Affecting Oral Drug Absorption-Part II: Gastrointestinal Transit Time, The AAPS journal, 18 (2016) 1322-1333.
[61] C. Kenyon, G. Hooper, D. Tierney, J. Butler, J. Devane, I. Wilding, The effect of food on the gastrointestinal transit and systemic absorption of naproxen from a novel sustained release formulation, Journal of controlled release, 34 (1995) 31-36.
[62] K.H. Yuen, A.A. Deshmukh, J.M. Newton, M. Short, R. Melchor, Gastrointestinal transit and absorption of theophylline from a multiparticulate controlled release formulation, International Journal of Pharmaceutics, 97 (1993) 61-77.
[63] G. Clarke, J. Newton, M. Short, Comparative gastrointestinal transit of pellet systems of varying density, International journal of pharmaceutics, 114 (1995) 1-11.
[64] G. Clarke, J. Newton, M. Short, Gastrointestinal transit of pellets of differing size and density, International journal of pharmaceutics, 100 (1993) 81-92.
[65] B. Abrahamsson, M. Alpsten, U.E. Jonsson, P. Lundberg, A. Sandberg, M. Sundgren, A. Svenheden, J. Tölli, Gastro-intestinal transit of a multiple-unit formulation (metoprolol CR/ZOK) and a non-disintegrating tablet with the emphasis on colon, International journal of pharmaceutics, 140 (1996) 229-235.
[66] A. Coupe, S. Davis, D. Evans, I. Wilding, Do pellet formulations empty from the stomach with food?, International journal of pharmaceutics, 92 (1993) 167-175.
[67] A.J. Coupe, S.S. Davis, I.R. Wilding, Variation in gastrointestinal transit of pharmaceutical dosage forms in healthy subjects, Pharm Res, 8 (1991) 360-364.
[68] S. Davis, J. Hardy, M. Taylor, D. Whalley, C. Wilson, The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet), International journal of pharmaceutics, 21 (1984) 331-340.
[69] F. Christensen, S. Davis, J. Hardy, M. Taylor, D. Whalley, C. Wilson, The use of gamma scintigraphy to follow the gastrointestinal transit of pharmaceutical formulations, Journal of pharmacy and pharmacology, 37 (1985) 91-95.
[70] K. Ewe, A.G. Press, S. Bollen, I. Schuhn, Gastric emptying of indigestible tablets in relation to composition and time of ingestion of meals studied by metal detector, Digestive diseases and sciences, 36 (1991) 146-152.
[71] H.M. Fadda, E.L. McConnell, M.D. Short, A.W. Basit, Meal-induced acceleration of tablet transit through the human small intestine, Pharmaceutical research, 26 (2009) 356-360.
[72] R. Khosla, S. Davis, Gastric emptying and small and large bowel transit of non-disintegrating tablets in fasted subjects, International journal of pharmaceutics, 52 (1989) 1-10.

[73] N. Billa, K.-H. Yuen, M.A.A. Khader, A. Omar, Gamma-scintigraphic study of the gastrointestinal transit and in vivo dissolution of a controlled release diclofenac sodium formulation in xanthan gum matrices, International journal of pharmaceutics, 201 (2000) 109-120.
[74] W. Weitschies, R.-S. Wedemeyer, O. Kosch, K. Fach, S. Nagel, E. Söderlind, L. Trahms, B. Abrahamsson, H. Mönnikes, Impact of the intragastric location of extended release tablets on food interactions, Journal of controlled release, 108 (2005) 375-385.
[75] F. Podczeck, N. Course, J. Newton, M. Short, The influence of non-disintegrating tablet dimensions and density on their gastric emptying in fasted volunteers, Journal of pharmacy and pharmacology, 59 (2007) 23-27.
[76] V.C. Ibekwe, H.M. Fadda, E.L. McConnell, M.K. Khela, D.F. Evans, A.W. Basit, Interplay between intestinal pH, transit time and feed status on the in vivo performance of pH responsive ileo-colonic release systems, Pharmaceutical research, 25 (2008) 1828-1835.
[77] J.C. Maublant, M. Sournac, J.-M. Aiache, A. Veyre, Dissolution rate and transit times of technetium-99m DTPA-labeled tablets, Journal of nuclear medicine, 28 (1987) 1199-1203.
[78] S. Davis, J. Hardy, C. Wilson, L. Feely, K. Palin, Gastrointestinal transit of a controlled release naproxen tablet formulation, International journal of pharmaceutics, 32 (1986) 85-90.
[79] P. Mojaverian, J.C. Reynolds, A. Ouyang, F. Wirth, P.E. Kellner, P.H. Vlasses, Mechanism of gastric emptying of a nondisintegrating radiotelemetry capsule in man, Pharmaceutical research, 8 (1991) 97-100.
[80] D. Cassilly, S. Kantor, L. Knight, A. Maurer, R. Fisher, J. Semler, H. Parkman, Gastric emptying of a non-digestible solid: assessment with simultaneous SmartPill pH and pressure capsule, antroduodenal manometry, gastric emptying scintigraphy, Neurogastroenterology & Motility, 20 (2008) 311-319.
[81] D. Lalezari, Gastrointestinal pH profile in subjects with irritable bowel syndrome, Annals of gastroenterology, 25 (2012) 333.
[82] C.A. Youngberg, R.R. Berardi, W.F. Howatt, M.L. Hyneck, G.L. Amidon, J.H. Meyer, J.B. Dressman, Comparison of gastrointestinal pH in cystic fibrosis and healthy subjects, Digestive diseases and sciences, 32 (1987) 472-480.
[83] J.M. Maurer, R.C. Schellekens, H.M. Van Rieke, C. Wanke, V. Iordanov, F. Stellaard, K.D. Wutzke, G. Dijkstra, M. van der Zee, H.J. Woerdenbag, Gastrointestinal pH and transit time profiling in healthy volunteers using the IntelliCap system confirms ileo-colonic release of ColoPulse tablets, PLoS One, 10 (2015) e0129076.
[84] S. Davis, F. Norring-Christensen, R. Khosla, L. Feely, Gastric emptying of large single unit dosage forms, Journal of pharmacy and pharmacology, 40 (1988) 205-207.
[85] K. Goodman, L.A. Hodges, J. Band, H.N. Stevens, W. Weitschies, C.G. Wilson, Assessing gastrointestinal motility and disintegration profiles of magnetic tablets by a novel magnetic imaging device and gamma scintigraphy, European journal of pharmaceutics and biopharmaceutics, 74 (2010) 84-92.
[86] C. Tuleu, C. Andrieux, P. Boy, J.C. Chaumeil, Gastrointestinal transit of pellets in rats: effect of size and density, International Journal of Pharmaceutics, 180 (1999) 123-131.
[87] J. Heinämäki, M. Marvola, I. Happonen, E. Westermarck, The fate of multiple-unit enteric-coated formulations in the stomach of the dog, International Journal of Pharmaceutics, 42 (1988) 105-115.
[88] R.L. Oberle, H. Das, Variability in gastric pH and delayed gastric emptying in yucatan miniature pigs, Pharmaceutical Research, 11 (1994) 592-594.
[89] C.P. Dooley, C. Di Lorenzo, J.E. Valenzuela, Variability of migrating motor complex in humans, Digestive diseases and sciences, 37 (1992) 723-728.
[90] E. Deloose, P. Janssen, I. Depoortere, J. Tack, The migrating motor complex: control mechanisms and its role in health and disease, Nature Reviews Gastroenterology & Hepatology, 9 (2012) 271-285.

[91] B. Laulicht, A. Tripathi, V. Schlageter, P. Kucera, E. Mathiowitz, Understanding gastric forces calculated from high-resolution pill tracking, Proceedings of the National Academy of Sciences, 107 (2010) 8201-8206.
[92] M. Kamba, Y. Seta, A. Kusai, K. Nishimura, Evaluation of the mechanical destructive force in the stomach of dog, International Journal of Pharmaceutics, 228 (2001) 209-217.
[93] P.P. Lopez, S. Gogna, A. Khorasani-Zadeh, Anatomy, Abdomen and Pelvis, Duodenum, StatPearls, Treasure Island (FL), 2021.
[94] J. Campbell, J. Berry, Y. Liang, Anatomy and Physiology of the Small Intestine, Shackelford's Surgery of the Alimentary Tract, 2 Volume Set2019, pp. 817-841.
[95] Small Intestine: Imaging Approach and Differential Diagnosis, Imaging in Gastroenterology2018, pp. 200-203.
[96] J. Feher, 8.3 - Intestinal and Colonic Chemoreception and Motility, in: J. Feher (Ed.) Quantitative Human Physiology (Second Edition), Academic Press, Boston, 2017, pp. 796-809.
[97] H.F. Helander, L. Fändriks, Surface area of the digestive tract - revisited, Scandinavian journal of gastroenterology, 49 (2014) 681-689.
[98] S. Nath, S. Das, o. Kar, K. Afrin, A. Dash, S. Akter, Topographical and biometrical anatomy of the digestive tract of White New Zealand Rabbit (Oryctolagus cuniculus), Journal of Advanced Veterinary and Animal Research, 3 (2016) 145.
[99] G. Gabella, The number of neurons in the small intestine of mice, guinea-pigs and sheep, Neuroscience, 22 (1987) 737-752.
[100] M. Koziolek, M. Grimm, D. Becker, V. Iordanov, H. Zou, J. Shimizu, C. Wanke, G. Garbacz, W. Weitschies, Investigation of pH and Temperature Profiles in the GI Tract of Fasted Human Subjects Using the Intellicap® System, Journal of Pharmaceutical Sciences, 104 (2015) 2855-2863.
[101] R.F. McCloy, G.R. Greenberg, J.H. Baron, Duodenal pH in health and duodenal ulcer disease: effect of a meal, Coca-Cola, smoking, and cimetidine, Gut, 25 (1984) 386-392.
[102] S.J. Rune, K. Viskum, Duodenal pH values in normal controls and in patients with duodenal ulcer, Gut, 10 (1969) 569-571.
[103] D.F. Evans, G. Pye, R. Bramley, A.G. Clark, T.J. Dyson, J.D. Hardcastle, Measurement of gastrointestinal pH profiles in normal ambulant human subjects, Gut, 29 (1988) 1035-1041.
[104] J. Fallingborg, P. Pedersen, B.A. Jacobsen, Small intestinal transit time and intraluminal pH in ileocecal resected patients with Crohn's disease, Dig Dis Sci, 43 (1998) 702-705.
[105] Raimundo AH, Evans DF, R. J, Gastrointestinal pH profiles in ulcerative colitis, Gastroenterology, 102 (1992) 681.
[106] R.L. Bown, J.A. Gibson, G.E. Sladen, B. Hicks, A.M. Dawson, Effects of lactulose and other laxatives on ileal and colonic pH as measured by a radiotelemetry device, Gut, 15 (1974) 999-1004.
[107] C.A. Youngberg, J. Wlodyga, S. Schmaltz, J.B. Dressman, Radiotelemetric determination of gastrointestinal pH in four healthy Beagles, American Journal of Veterinary Research, 46 (1985) 1516-1521.
[108] R. Khosla, L.C. Feely, S.S. Davis, Gastrointestinal transit of non-disintegrating tablets in fed subjects, International Journal of Pharmaceutics, 53 (1989) 107-117.
[109] A.E. Mikolajczyk, S. Watson, B.L. Surma, D.T. Rubin, Assessment of Tandem Measurements of pH and Total Gut Transit Time in Healthy Volunteers, Clin Transl Gastroenterol, 6 (2015) e100-e100.
[110] J.B. Dressman, Comparison of Canine and Human Gastrointestinal Physiology, Pharmaceutical Research, 3 (1986) 123-131.
[111] S.S. Davis, L. Illum, M. Hinchcliffe, Gastrointestinal transit of dosage forms in the pig, Journal of Pharmacy and Pharmacology, 53 (2010) 33-39.
[112] V. Snoeck, N. Huyghebaert, E. Cox, A. Vermeire, J. Saunders, J.P. Remon, F. Verschooten, B.M. Goddeeris, Gastrointestinal transit time of nondisintegrating radio-opaque pellets in suckling and recently weaned piglets, J Control Release, 94 (2004) 143-153.

[113] K. Ikegami, K. Tagawa, S. Narisawa, T. Osawa, Suitability of the Cynomolgus Monkey as an Animal Model for Drug Absorption Studies of Oral Dosage Forms from the Viewpoint of Gastrointestinal Physiology, Biological and Pharmaceutical Bulletin, 26 (2003) 1442-1447.
[114] H. Kondo, Y. Takahashi, T. Watanabe, S. Yokohama, J. Watanabe, Gastrointestinal transit of liquids in unfed cynomolgus monkeys, Biopharmaceutics & Drug Disposition, 24 (2003) 131-140.
[115] G. Le Blay, C. Michel, H.M. Blottière, C. Cherbut, Enhancement of butyrate production in the rat caecocolonic tract by long-term ingestion of resistant potato starch, British Journal of Nutrition, 82 (1999) 419-426.
[116] T. Sawamoto, S. Haruta, Y. Kurosaki, K. Higaki, T. Kimura, Prediction of the Plasma Concentration Profiles of Orally Administered Drugs in Rats on the Basis of Gastrointestinal Transit Kinetics and Absorbability, Journal of Pharmacy and Pharmacology, 49 (2011) 450-457.
[117] S.S. Davis, E.A. Wilding, I.R. Wilding, Gastrointestinal transit of a matrix tablet formulation: comparison of canine and human data, International Journal of Pharmaceutics, 94 (1993) 235-238.
[118] J.A. Lidbury, J.S. Suchodolski, R. Ivanek, J.M. Steiner, Assessment of the Variation Associated with Repeated Measurement of Gastrointestinal Transit Times and Assessment of the Effect of Oral Ranitidine on Gastrointestinal Transit Times Using a Wireless Motility Capsule System in Dogs, Veterinary Medicine International, 2012 (2012) 938417.
[119] R.R. Davies, J.A.E. Rees Davies, Rabbit gastrointestinal physiology, Veterinary Clinics of North America: Exotic Animal Practice, 6 (2003) 139-153.
[120] J. Berghausen, F.H. Seiler, N. Gobeau, B. Faller, Simulated rat intestinal fluid improves oral exposure prediction for poorly soluble compounds over a wide dose range, ADMET & DMPK, 4 (2016) 35-53.
[121] M. Arndt, H. Chokshi, K. Tang, N.J. Parrott, C. Reppas, J.B. Dressman, Dissolution media simulating the proximal canine gastrointestinal tract in the fasted state, European Journal of Pharmaceutics and Biopharmaceutics, 84 (2013) 633-641.
[122] L.J. Henze, N.J. Koehl, R. Jansen, R. Holm, M. Vertzoni, P.D. Whitfield, B.T. Griffin, Development and evaluation of a biorelevant medium simulating porcine gastrointestinal fluids, European Journal of Pharmaceutics and Biopharmaceutics, 154 (2020) 116-126.
[123] H.A. Merchant, F. Afonso-Pereira, S.C. Rabbie, S.A. Youssef, A.W. Basit, Gastrointestinal characterisation and drug solubility determination in animals, The Journal of pharmacy and pharmacology, 67 (2015) 630-639.
[124] L. Kalantzi, E. Persson, B. Polentarutti, B. Abrahamsson, K. Goumas, J.B. Dressman, C. Reppas, Canine intestinal contents vs. simulated media for the assessment of solubility of two weak bases in the human small intestinal contents, Pharm Res, 23 (2006) 1373-1381.
[125] R.P. Harpur, J.S. Popkin, Osmolality of Blood and Intestinal Contents in the Pig, Guinea Pig, and Ascaris Lumbricoides, Canadian Journal of Biochemistry, 43 (1965) 1157-1169.
[126] K. Tasaka, J.T. Farrar, Intraluminal pressure of the small intestine of the unanesthetized dog, Pflügers Archiv, 364 (1976) 35-44.
[127] G. Bogeski, A.D. Shafton, P.D. Kitchener, D.M. Ferens, J.B. Furness, A quantitative approach to recording peristaltic activity from segments of rat small intestine in vivo, Neurogastroenterol Motil, 17 (2005) 262-272.
[128] M.L. Siegle, S. Bühner, M. Schemann, H.R. Schmid, H.J. Ehrlein, Propagation velocities and frequencies of contractions along canine small intestine, The American journal of physiology, 258 (1990) G738-744.
[129] J.H. Szurszewski, A migrating electric complex of canine small intestine, American Journal of Physiology-Legacy Content, 217 (1969) 1757-1763.
[130] M. Ruckebusch, J. Fioramonti, Electrical spiking activity and propulsion in small intestine in fed and fasted rats, Gastroenterology, 68 (1975) 1500-1508.
[131] M. Kamba, Y. Seta, A. Kusai, K. Nishimura, Comparison of the mechanical destructive force in the small intestine of dog and human, International Journal of Pharmaceutics, 237 (2002) 139-149.

[132] G.I. Sandle, Salt and water absorption in the human colon: a modern appraisal, Gut, 43 (1998) 294-299.
[133] R. Bartolí, J. Boix, G. Odena, N.D. De la Ossa, V.M. de Vega, V. Lorenzo-Zúñiga, Colonoscopy in rats: An endoscopic, histological and tomographic study, World J Gastrointest Endosc, 5 (2013) 226-230.
[134] H.A. Merchant, S.C. Rabbie, F.J.O. Varum, F. Afonso-Pereira, A.W. Basit, Influence of ageing on the gastrointestinal environment of the rat and its implications for drug delivery, European Journal of Pharmaceutical Sciences, 62 (2014) 76-85.
[135] L. Ogiolda, R. Wanke, O. Rottmann, W. Hermanns, E. Wolf, Intestinal dimensions of mice divergently selected for body weight, The Anatomical Record, 250 (1998) 292-299.
[136] C. Casteleyn, A. Rekecki, A. Van Der Aa, P. Simoens, W. Van Den Broeck, Surface area assessment of the murine intestinal tract as a prerequisite for oral dose translation from mouse to man, Laboratory Animals, 44 (2010) 176-183.
[137] H.A. Merchant, E.L. McConnell, F. Liu, C. Ramaswamy, R.P. Kulkarni, A.W. Basit, S. Murdan, Assessment of gastrointestinal pH, fluid and lymphoid tissue in the guinea pig, rabbit and pig, and implications for their use in drug development, European Journal of Pharmaceutical Sciences, 42 (2011) 3-10.
[138] K. Arslan, I. Coskun, B. Yıldız, A Geometric Modeling of Dog Intestine, Turkish Journal of Veterinary and Animal Sciences, 30 (2006) 483-488.
[139] A. McGrosky, C. Meloro, A. Navarrete, S.A. Heldstab, A.C. Kitchener, K. Isler, M. Clauss, Gross intestinal morphometry and allometry in primates, American Journal of Primatology, 81 (2019) e23035.
[140] J.E. Lambert, Primate digestion: Interactions among anatomy, physiology, and feeding ecology, Evolutionary Anthropology: Issues, News, and Reviews, 7 (1998) 8-20.
[141] J. Hecker, W. Grovum, Rates of Passage of Digesta and Water Absorption along the Large Intestines of Sheep, Cows and Pigs, Australian Journal of Biological Sciences, 28 (1975) 161-168.
[142] N.F. Shroyer, S.A. Kocoshis, 31 - Anatomy and Physiology of the Small and Large Intestines, in: R. Wyllie, J.S. Hyams (Eds.) Pediatric Gastrointestinal and Liver Disease (Fourth Edition), W.B. Saunders, Saint Louis, 2011, pp. 324-336.e322.
[143] S. Sulaiman, L. Marciani, MRI of the Colon in the Pharmaceutical Field: The Future before us, Pharmaceutics, 11 (2019) 146.
[144] F.J.O. Varum, F. Veiga, J.S. Sousa, A.W. Basit, Mucus thickness in the gastrointestinal tract of laboratory animals, Journal of Pharmacy and Pharmacology, 64 (2012) 218-227.
[145] L. Dou, F.K.H. Gavins, Y. Mai, C.M. Madla, F. Taherali, M. Orlu, S. Murdan, A.W. Basit, Effect of Food and an Animal's Sex on P-Glycoprotein Expression and Luminal Fluids in the Gastrointestinal Tract of Wistar Rats, Pharmaceutics, 12 (2020) 296.
[146] F. Afonso-Pereira, L. Dou, S.J. Trenfield, C.M. Madla, S. Murdan, J. Sousa, F. Veiga, A.W. Basit, Sex differences in the gastrointestinal tract of rats and the implications for oral drug delivery, European Journal of Pharmaceutical Sciences, 115 (2018) 339-344.
[147] E. Sjögren, B. Abrahamsson, P. Augustijns, D. Becker, M.B. Bolger, M. Brewster, J. Brouwers, T. Flanagan, M. Harwood, C. Heinen, R. Holm, H.-P. Juretschke, M. Kubbinga, A. Lindahl, V. Lukacova, U. Münster, S. Neuhoff, M.A. Nguyen, A.v. Peer, C. Reppas, A.R. Hodjegan, C. Tannergren, W. Weitschies, C. Wilson, P. Zane, H. Lennernäs, P. Langguth, In vivo methods for drug absorption – Comparative physiologies, model selection, correlations with in vitro methods (IVIVC), and applications for formulation/API/excipient characterization including food effects, European Journal of Pharmaceutical Sciences, 57 (2014) 99-151.
[148] D.J. Chivers, C.M. Hladik, Morphology of the gastrointestinal tract in primates: Comparisons with other mammals in relation to diet, Journal of Morphology, 166 (1980) 337-386.
[149] W.O. Kirwan, A.N. Smith, W.D. Mitchell, J.D. Falconer, M.A. Eastwood, Bile acids and colonic motility in the rabbit and the human, Gut, 16 (1975) 894-902.

[150] D.M. Grayzel, E.G. Miller, The pH of the Contents of the Gastrointestinal Tract in Dogs, in relation to Diet and Rickets, Journal of Biological Chemistry, 76 (1928) 423-436.
[151] R.A. Argenzio, H.W. Moon, L.J. Kemeny, S.C. Whipp, Colonic compensation in transmissible gastroenteritis of swine, Gastroenterology, 86 (1984) 1501-1509.
[152] V. Theodorou, J. Fioramonti, L. Buéno, WATER ABSORPTION FROM THE PIG PROXIMAL COLON: RELATIONS WITH FEEDING AND FLOW OF DIGESTA, Quarterly Journal of Experimental Physiology, 74 (1989) 521-529.
[153] A. Diakidou, M. Vertzoni, K. Goumas, E. Söderlind, B. Abrahamsson, J. Dressman, C. Reppas, Characterization of the Contents of Ascending Colon to Which Drugs are Exposed After Oral Administration to Healthy Adults, Pharmaceutical Research, 26 (2009) 2141-2151.
[154] C. Reppas, E. Karatza, C. Goumas, C. Markopoulos, M. Vertzoni, Characterization of Contents of Distal Ileum and Cecum to Which Drugs/Drug Products are Exposed During Bioavailability/Bioequivalence Studies in Healthy Adults, Pharmaceutical Research, 32 (2015) 3338-3349.
[155] M. Vertzoni, K. Goumas, E. Söderlind, B. Abrahamsson, J.B. Dressman, A. Poulou, C. Reppas, Characterization of the Ascending Colon Fluids in Ulcerative Colitis, Pharmaceutical Research, 27 (2010) 1620-1626.
[156] H.M. Fadda, T. Sousa, A.S. Carlsson, B. Abrahamsson, J.G. Williams, D. Kumar, A.W. Basit, Drug solubility in luminal fluids from different regions of the small and large intestine of humans, Mol Pharm, 7 (2010) 1527-1532.
[157] A. Ziegler, L. Gonzalez, A. Blikslager, Large Animal Models: The Key to Translational Discovery in Digestive Disease Research, Cellular and Molecular Gastroenterology and Hepatology, 2 (2016) 716-724.
[158] G.K. Nandhra, E.B. Mark, G.L. Di Tanna, A.-M. Haase, J. Poulsen, S. Christodoulides, V. Kung, M.W. Klinge, K. Knudsen, P. Borghammer, K.O. Andersen, L. Fynne, N. Sutter, V. Schlageter, K. Krogh, A.M. Drewes, M. Birch, S.M. Scott, Normative values for region-specific colonic and gastrointestinal transit times in 111 healthy volunteers using the 3D-Transit electromagnet tracking system: Influence of age, gender, and body mass index, Neurogastroenterology & Motility, 32 (2020) e13734.
[159] J.M. Hinton, J.E. Lennard-Jones, A.C. Young, A new method for studying gut transit times using radioopaque markers, Gut, 10 (1969) 842-847.
[160] P. Arhan, G. Devroede, B. Jehannin, M. Lanza, C. Faverdin, C. Dornic, B. Persoz, L. Tétreault, B. Perey, D. Pellerin, Segmental colonic transit time, Dis Colon Rectum, 24 (1981) 625-629.
[161] A.M. Metcalf, S.F. Phillips, A.R. Zinsmeister, R.L. MacCarty, R.W. Beart, B.G. Wolff, Simplified assessment of segmental colonic transit, Gastroenterology, 92 (1987) 40-47.
[162] R. Sadik, P.O. Stotzer, M. Simrén, H. Abrahamsson, Gastrointestinal transit abnormalities are frequently detected in patients with unexplained GI symptoms at a tertiary centre, Neurogastroenterology and Motility, 20 (2008) 197-205.
[163] H. Abrahamsson, S. Antov, Accuracy in assessment of colonic transit time with particles: how many markers should be used?, Neurogastroenterology & Motility, 22 (2010) 1164-1169.
[164] S.S.C. Rao, Constipation: Evaluation and Treatment of Colonic and Anorectal Motility Disorders, Gastroenterology Clinics of North America, 36 (2007) 687-711.
[165] M. Proano, M. Camilleri, S.F. Phillips, M.L. Brown, G.M. Thomforde, Transit of solids through the human colon: regional quantification in the unprepared bowel, American Journal of Physiology-Gastrointestinal and Liver Physiology, 258 (1990) G856-G862.
[166] M. Camilleri, A.R. Zinsmeister, Towards a relatively inexpensive, noninvasive, accurate test for colonic motility disorders, Gastroenterology, 103 (1992) 36-42.
[167] E.S. Bonapace, A.H. Maurer, S. Davidoff, B. Krevsky, R.S. Fisher, H.P. Parkman, Whole gut transit scintigraphy in the clinical evaluation of patients with upper and lower gastrointestinal symptoms, The American Journal of Gastroenterology, 95 (2000) 2838-2847.

[168] A. Deiteren, M. Camilleri, D. Burton, S. McKinzie, A. Rao, A.R. Zinsmeister, Effect of meal ingestion on ileocolonic and colonic transit in health and irritable bowel syndrome, Dig Dis Sci, 55 (2010) 384-391.
[169] A. Deiteren, M. Camilleri, A.E. Bharucha, D. Burton, S. Mckinzie, A.S. Rao, A.R. Zinsmeister, Performance characteristics of scintigraphic colon transit measurement in health and irritable bowel syndrome and relationship to bowel functions, Neurogastroenterology & Motility, 22 (2010) 415-e495.
[170] S. Nullens, T. Nelsen, M. Camilleri, D. Burton, D. Eckert, J. Iturrino, M. Vazquez-Roque, A.R. Zinsmeister, Regional colon transit in patients with dys-synergic defaecation or slow transit in patients with constipation, Gut, 61 (2012) 1132-1139.
[171] A.R. Zinsmeister, D. Burton, M. Camilleri, Pharmacodynamic and clinical endpoints for functional colonic disorders: statistical considerations, Dig Dis Sci, 58 (2013) 509-518.
[172] G.J. Kolar, M. Camilleri, D. Burton, A. Nadeau, A.R. Zinsmeister, Prevalence of colonic motor or evacuation disorders in patients presenting with chronic nausea and vomiting evaluated by a single gastroenterologist in a tertiary referral practice, Neurogastroenterology & Motility, 26 (2014) 131-138.
[173] M.R. von der Ohe, M. Camilleri, L.K. Kvols, G.M. Thomforde, Motor dysfunction of the small bowel and colon in patients with the carcinoid syndrome and diarrhea, N Engl J Med, 329 (1993) 1073-1078.
[174] M. Camilleri, S. McKinzie, I. Busciglio, P.A. Low, S. Sweetser, D. Burton, K. Baxter, M. Ryks, A.R. Zinsmeister, Prospective study of motor, sensory, psychologic, and autonomic functions in patients with irritable bowel syndrome, Clin Gastroenterol Hepatol, 6 (2008) 772-781.
[175] M. Camilleri, Review article: biomarkers and personalised therapy in functional lower gastrointestinal disorders, Alimentary pharmacology & therapeutics, 42 (2015) 818-828.
[176] S.S. Rao, B. Kuo, R.W. McCallum, W.D. Chey, J.K. DiBaise, W.L. Hasler, K.L. Koch, J.M. Lackner, C. Miller, R. Saad, J.R. Semler, M.D. Sitrin, G.E. Wilding, H.P. Parkman, Investigation of colonic and whole-gut transit with wireless motility capsule and radiopaque markers in constipation, Clin Gastroenterol Hepatol, 7 (2009) 537-544.
[177] M. Camilleri, N.K. Thorne, Y. Ringel, W.L. Hasler, B. Kuo, T. Esfandyari, A. Gupta, S.M. Scott, R.W. Mccallum, H.P. Parkman, E. Soffer, G.E. Wilding, J.R. Semler, S.S.c. Rao, Wireless pH-motility capsule for colonic transit: prospective comparison with radiopaque markers in chronic constipation, Neurogastroenterology & Motility, 22 (2010) 874-e233.
[178] W.L. Hasler, R.J. Saad, S.S. Rao, G.E. Wilding, H.P. Parkman, K.L. Koch, R.W. McCallum, B. Kuo, I. Sarosiek, M.D. Sitrin, J.R. Semler, W.D. Chey, Heightened colon motor activity measured by a wireless capsule in patients with constipation: relation to colon transit and IBS, Am J Physiol Gastrointest Liver Physiol, 297 (2009) G1107-1114.
[179] C.E. Brinck, E.B. Mark, M.W. Klinge, C. Ejerskov, N. Sutter, V. Schlageter, S.M. Scott, A.M. Drewes, K. Krogh, Magnetic tracking of gastrointestinal motility, Physiological Measurement, 41 (2020) 12TR01.
[180] E. Stathopoulos, V. Schlageter, B. Meyrat, Y. de Ribaupierre, P. Kucera, Magnetic pill tracking: a novel non-invasive tool for investigation of human digestive motility, Neurogastroenterology & Motility, 17 (2005) 148-154.
[181] J. Worsøe, L. Fynne, T. Gregersen, V. Schlageter, L.A. Christensen, J.F. Dahlerup, N.J.M. Rijkhoff, S. Laurberg, K. Krogh, Gastric transit and small intestinal transit time and motility assessed by a magnet tracking system, BMC Gastroenterology, 11 (2011) 145.
[182] Y.K. Cho, S.C. Kim, K.C. Lee, Radiographie estimation of colonie transit time with kolomark™ in normal Dogs, Journal of Veterinary Clinics, 29 (2012) 237-241.
[183] V. Snoeck, N. Huyghebaert, E. Cox, A. Vermeire, J. Saunders, J.P. Remon, F. Verschooten, B.M. Goddeeris, Gastrointestinal transit time of nondisintegrating radio-opaque pellets in suckling and recently weaned piglets, Journal of Controlled Release, 94 (2004) 143-153.

[184] F. Pomerri, G. Dodi, M. Nardin, P.C. Muzzio, Colonic total and segmental transit times in healthy Italian adults, La radiologia medica, 114 (2009) 925-934.
[185] B.K. Song, K.O. Cho, Y. Jo, J.W. Oh, Y.S. Kim, Colon transit time according to physical activity level in adults, Journal of neurogastroenterology and motility, 18 (2012) 64-69.
[186] M. Bouchoucha, G. Devroede, A. Faye, P. Le Toumelin, P. Arhan, M. Arsac, Colonic response to food in constipation, International Journal of Colorectal Disease, 21 (2006) 826-833.
[187] M. Zhi, Z. Zhou, H. Chen, F. Xiong, J. Huang, H. He, M. Zhang, M. Su, X. Gao, P. Hu, Clinical application of a gadolinium-based capsule as an MRI contrast agent in slow transit constipation diagnostics, Neurogastroenterology & Motility, 29 (2017) e13020.
[188] F. Schneider, M. Grimm, M. Koziolek, C. Modeß, A. Dokter, T. Roustom, W. Siegmund, W. Weitschies, Resolving the physiological conditions in bioavailability and bioequivalence studies: Comparison of fasted and fed state, European Journal of Pharmaceutics and Biopharmaceutics, 108 (2016) 214-219.
[189] G.K. Kalsi, D. Grønlund, J. Martin, A.M. Drewes, S.M. Scott, M.J. Birch, Technical report: Inter- and intra-rater reliability of regional gastrointestinal transit times measured using the 3D-Transit electromagnet tracking system, Neurogastroenterology & Motility, 30 (2018) e13396.
[190] S. Buhmann, C. Kirchhoff, R. Ladurner, T. Mussack, M.F. Reiser, A. Lienemann, Assessment of colonic transit time using MRI: a feasibility study, European Radiology, 17 (2007) 669-674.
[191] E.B. Mark, J.L. Poulsen, A.-M. Haase, M. Espersen, T. Gregersen, V. Schlageter, S.M. Scott, K. Krogh, A.M. Drewes, Ambulatory assessment of colonic motility using the electromagnetic capsule tracking system, Neurogastroenterology & Motility, 31 (2019) e13451.
[192] Y.-K. CHAN, A.C.-P. KWAN, H. YUEN, Y.-W. YEUNG, K.-C. LAI, J. WU, G.S.-W. WONG, C.-M. LEUNG, W.-C. CHEUNG, C.-K. WONG, Normal colon transit time in healthy Chinese adults in Hong Kong, Journal of Gastroenterology and Hepatology, 19 (2004) 1270-1275.
[193] E. Danquechin Dorval, J.P. Barbieux, L. Picon, D. Alison, P. Codjovi, P. Rouleau, [Simplified measurement of colonic transit time by one radiography of the abdomen and a single type of marker. Normal values in 82 volunteers related to the sexes], Gastroenterol Clin Biol, 18 (1994) 141-144.
[194] M. Bouchoucha, G. Devroede, E. Dorval, A. Faye, P. Arhan, M. Arsac, Different segmental transit times in patients with irritable bowelsyndrome and “normal” colonic transit time: is there a correlation withsymptoms?, Techniques in Coloproctology, 10 (2006) 287-296.
[195] M. Bouchoucha, G. Devroede, P. Arhan, B. Strom, J. Weber, P.-H. Cugnenc, P. Denis, J.-P. Barbier, What is the meaning of colorectal transit time measurement?, Diseases of the Colon & Rectum, 35 (1992).
[196] D.C. Hernot, H.J. Dumon, V.C. Biourge, L.J. Martin, P.G. Nguyen, Evaluation of association between body size and large intestinal transit time in healthy dogs, Am J Vet Res, 67 (2006) 342-347.
[197] A.M. Haase, T. Gregersen, V. Schlageter, M.S. Scott, M. Demierre, P. Kucera, J.F. Dahlerup, K. Krogh, Pilot study trialling a new ambulatory method for the clinical assessment of regional gastrointestinal transit using multiple electromagnetic capsules, Neurogastroenterology & Motility, 26 (2014) 1783-1791.
[198] A.M. Haase, T. Gregersen, L.A. Christensen, J. Agnholt, J.F. Dahlerup, V. Schlageter, K. Krogh, Regional gastrointestinal transit times in severe ulcerative colitis, Neurogastroenterology & Motility, 28 (2016) 217-224.
[199] T. Gidenne, Y. Ruckebusch, A. Lapanouse, M. Segura, Flow and passage rate studies at the ileal level in the rabbit, Reprod. Nutr. Dev., 29 (1989) 403-412.
[200] H.J. Ehrlein, H. Reich, M. Schwinger, Colonic motility and transit of digesta during hard and soft faeces formation in rabbits, The Journal of Physiology, 338 (1983) 75-86.
[201] A.M. Robinson, A.A. Rahman, S.E. Carbone, S. Randall-Demllo, R. Filippone, J.C. Bornstein, R. Eri, K. Nurgali, Alterations of colonic function in the Winnie mouse model of spontaneous chronic colitis, American Journal of Physiology-Gastrointestinal and Liver Physiology, 312 (2017) G85-G102.

[202] H.H. Huang, C.H. Ting, Y.F. Syu, S.C. Chang, C.Y. Chen, Correlation between colonic secretion and colonic motility in rats: Role of ghrelin, World J Gastroenterol, 22 (2016) 10140-10147.