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Characterization of gastrointestinal transit and luminal conditions in pigs using a telemetric motility capsule

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A B S T R A C T

Within preclinical research, the pig has become an important model in regulatory toxicology and pharmacokinetics, to assess oral dosage forms and to compare different formulation strategies. In addition, there are emerging application of the pig model to asses clinical dosing conditions in the fasted and fed state. In this study, the gastrointestinal transit conditions in male landrace pigs were studied with a telemetric motility capsule under fasted and postprandial conditions. The whole gut transit time (WGTT) was determined by administering a SmartPill® capsule to four landrace pigs, under both fasted and fed state conditions in a cross-over study design. Overall, this study found that small intestinal transit in landrace pigs ranged from 2.3 – 4.0 h, and was broadly similar to reported human estimates and was not affected by the intake conditions. Gastric emptying was highly variable and prolonged in landrace pigs ranging from 20 – 233 h and up to 264 h in one specific case. Under dynamic conditions pigs have a low gastric pH comparable to humans, however a high variability under fasted conditions could be observed. The comparison of the data from this study with a recent similar study in beagle dogs revealed major differences between gastric maximum pressures observed in landrace pigs and dogs. In the porcine stomach maximum pressures of up to 402 mbar were observed, which are comparable to reported human data. Intestinal maximum pressures in landrace pigs were in the same range as in humans. Overall, the study provides new insights of gastrointestinal conditions in landrace pigs, which can lead to more accurate interpretation of *in vivo* results obtained of pharmacokinetic studies in preclinical models. While small intestinal transit conditions, GI pH and pressures were similar to humans, the prolonged gastric emptying observed in pigs need to be considered in assessing the suitability of the pig model for assessing *in vivo* performance of large non-disintegrated oral drug products.

1. Introduction

Over the last decade, pigs have been increasingly proposed as a preclinical model in regulatory toxicology and pharmacokinetics (Bode et al., 2010; Sjogren et al., 2014). A principle advantage of the pig model is the similarity between the anatomy and physiology of the gastrointestinal (GI) tract in humans and pigs. For example, the gastric pH in pigs and human is similar ranging from 1.15 – 4.0 in pigs and 1.0 – 3.5 in humans (Henze et al., 2018b). Pigs, like humans, are omnivorous and they have similar digestive system. Moreover, the intestinal microbiome of the colon and the digestion characteristics of the small intestines are considered to be similar to human (Henze et al., 2018b; Suenderhauf and Parrott, 2013; Swindle and Smith, 1998). The pig model has previously been used to investigate various formulation strategies that enhance oral bioavailability of poorly water soluble drugs (Griffin et al., 2014; Henze et al., 2018b; McCarthy et al., 2017; O'Shea et al., 2015; Thomas et al., 2014). Furthermore, pigs have been shown to be suitable to explore food dependent bioavailability (Henze et al., 2019, 2020b), as well as novel gastro-retentive dosage forms (Brayden and Baird). The two most common breeds used in pharmaceutical research are landrace pigs and Göttingen minipigs and are therefore the most widely characterised physiologically (Bode et al., 2010; Henze et al., 2018b). In general, both breeds display similar GI physiology, albeit breed specific differences have been reported (Helke and Swindle, 2013). . Whereas historically dogs have been more commonly employed as a large animal model in preclinical drug development, and hence canine GI physiology has been extensively characterised in the literature (Hatton et al., 2015; Koziolek et al., 2019; Sjogren et al., 2014). In contrast, GI physiology of the pig is less well characterised. While it is clear that each preclinical species have their relative similarities and differences to human GI

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conditions, it is also imperative that a complete comparison of representative GI physiology is available for each preclinical species, using comparable techniques to those performed in humans. Therefore, while there is no 'ideal' preclinical model in terms of representing all aspects of human GI conditions, selection of the most appropriate species for evaluating a given drug product and/or dosage form should be informed by how closely it simulates human conditions.

Relative to humans, gastric transit times have been reported to be prolonged in pigs, although estimates of porcine gastric emptying have been reported to show high inter-individual and inter-study variability (Davis et al., 2001; Henze et al., 2018a; Hossain et al., 1990; Suenderhauf et al., 2014). As gastric transit time is a fundamental factor influencing drug absorption, it is crucial to get accurate insights into transit times, as well as pH and pressure profiles in pigs. To investigate these conditions, several techniques are available such as sampling of intestinal fluids, imaging techniques (scintigraphy) or telemetric capsules (Hens et al., 2017). One of the first published studies to explore gastric conditions in pigs involved the use of a telemetric capsule to investigate gastric emptying in Yucatan minipigs (Oberle and Das, 1994). This study provided first insights into GI conditions in pigs and reported similar pH ranges between pigs and humans, one pig displayed a prolonged gastric transit time (> 54 h). While the study was useful in terms of demonstrating a prolonged gastric transit in pigs, other key factors like the impact of a high-fat, high-caloric meal on GI transit were still lacking. An alternative technique to evaluate gastric emptying is the labelling of dosage forms with a suitable gamma-emitting radio nuclide, the GI transit of the dosage form can therefore be tracked using gamma scintigraphy. Davis *et al.* reported that gastric emptying time after a light meal ranged between 1.5 - 6 h in landrace pigs, based upon investigations of the gastric emptying of liquids and solid dosage forms in pigs using gamma scintigraphy (Davis et al., 2001). In a subsequent study by the same group, it was reported that the mean time to empty 50 % of a dosed liquid to be 1.4 h in pigs. The gastric emptying rate of pellets in pigs (pellet size of 0.85 -1.4 mm), was reported to be 2.2 h for 50 % of the pellets to enter the small intestine and 4 h after dosing a non-disintegrating tablet (Davis et al., 2001). Another approach, was the use of paracetamol to evaluate gastric emptying. Paracetamol is known to be poorly absorbed in the stomach, but rapidly absorbed upon entry into the small intestine, which makes it suitable marker when examining gastric emptying rate (Suenderhauf et al., 2014). In recent studies, the paracetamol absorption technique has been used to investigate gastric emptying in landrace pigs and Göttingen minipigs (Christiansen et al., 2015; Henze et al., 2018a; Henze et al., 2019). The pharmacokinetic results of paracetamol demonstrated no significant differences between fasted and fed state groups. Due to the lack of a difference between fasted and fed study groups, it was hypothesized that paracetamol may not represent a suitable marker of food induced changes in gastric emptying (Henze et al., 2019).

Apart from supporting formulation development, the pig model can also be used to predict food effect on oral drug bioavailability. We have recently reported that the food effect of fenofibrate and venetoclax can be reliably predicted with the aid of landrace pigs. Thereby, a key aspect was the establishment of a standardized food effect study protocol, utilizing the FDA style high-fat high-caloric meal to mimic postprandial conditions present in human food effect studies (Henze et al., 2019, 2020b). Understanding GI physiology under preclinical study conditions is crucial for the interpretation of the results obtained *in vivo*. The SmartPill® has recently been used to investigate canine and human GI conditions under fasted and fed state (high caloric meal). It is a non-invasive method to evaluate pH, temperature and pressure along the GI tract (Koziolek et al., 2019; Koziolek et al., 2015; Schneider et al., 2016). The SmartPill® is an ingestible capsule (26 × 13 mm), and facilitate live capture of data under dynamic conditions. To the best of our knowledge, the SmartPill® has not been used in pigs under conditions simulating preclinical porcine food effect studies.

The main objective of this work was to explore GI conditions in pigs by determining pH values, pressure and temperature by the use of a telemetric motility capsule (SmartPill®). Though this, the impact of food intake on the GI conditions was also investigated and compared with fasted state conditions. The secondary goal of this work was to compare the pig model to the more commonly used dog model, which will facilitate a more critical informed decision on which preclinical species to select in drug product development and investigation of formulation behaviour. Furthermore, the data from this study were compared to recent SmartPill® studies conducted in humans.

2. Materials and Methods

2.1. Materials

All food components used in preparing FDA recommended breakfast were purchased commercially and are listed in Table 1.

2.2. Telemetric motility capsule (TMC) system

The SmartPill® GI Monitoring system was used to measure GI conditions: (I) pH, (II) temperature, (III) pressure. Therefore, a data receiver was fixed close to each animal to record the data transferred from the capsule.

2.2.1. Calibration

Before the administration, the correct functioning of the capsules was verified in terms of pH, pressure and temperature. The intactness of the pressure sensor was tested over a range of 0 – 400 mbar with the aid of a manometer. A calibration with five different pH values ranging from pH 1.0 – 10.0 was used, using a calibrated pH meter (model 3510, JENWAY). After excretion, the same calibration procedure was used to account for the known drift of the pH sensor. The temperature sensor was checked with a one-point calibration at room temperature.

2.2.2. Data analysis

Temperature compensation for pH value and pressure was performed automatically by the corresponding MotiliGI® software. Also the baseline pressure was automatically corrected by the software. However, it was chosen to refrain from using these baseline corrected pressure data as these were only relative data, which did not represent the real values measured *in vivo*. Thus, only temperature compensated pressure and pH data as well as the original temperature data were used for data analysis. All datasets were analysed with the aid of Origin 8.5.1G (OriginLab Corp., Northampton, USA).

Gastric emptying time (GET), colonic arrival time (CAT) and small intestinal transit time (SITT), were determined by considering significant pH changes. Gastric emptying was identified by a significant permanent pH change to pH 5 or higher and maximum pressure events above 300 mbar (225 mmHg) as these are typically limited to the stomach (Koziolek et al., 2019). Colonic entry was identified by a sharp pH decrease of at least 0.5 pH units. Capsule secretion was identified by a drop in temperature.

As a consequence of the observed pH drift of the capsule sensor, the pH values were corrected based on the results of the post-calibration.

Table 1
Composition of high-fat, high-caloric meal fed to pigs in the current study

Component	Approximate weight (g)	Approximate total calories (kcal)
One slice of bacon	30	70
1 slice buttered toast	45	100
1 fried egg	60	92
4oz (118mL) whole milk	122.5	70
2oz hashed brown potatoes	57.5	112
Total	**315 g**	**444 kcal**

Following the equation 1

$$pH_{corr} = pH_m - \left(\frac{\Delta\, pH}{WGTT} * t\right) \quad (1)$$

where pH_m is the measure pH value by the capsule, Δ pH is the mean pH drift calculated from the values determined during calibration, which was performed before administration and after excretion, WGTT is the whole gut transit time in hours and t is the time in hours after the administration of the capsule. The small intestinal transit time (SITT) was normalized by the following equation:

$$SITT_{norm} = \frac{t - GET}{CAT - GET} \quad (2)$$

where $SITT_{norm}$ is the normalized small intestinal transit time in hours, t is the time in hours after capsule intake, GET is the gastric emptying time in hours, and CAT is the colon arrival time in hours. The data was characterised by minimum, maximum, range, median, arithmetic mean including the standard deviation where appropriate.

2.3. Animals

Male landrace pigs (15 – 17 kg) were sourced locally and housed individually at the University's Biological Services Unit. Throughout the study pigs were fed approximately 175 g of standard weanling pig pellet feed twice daily. Initially four pigs were enrolled in this study in a crossover design. However, an additionally four pigs were subsequently included, as in three pigs the SmartPill® was not emptied from the stomach until the battery was completely empty (P3, P6, P44) and one pig vomited after the administration of the telemetric capsule (P4) and has been excluded. For the remaining four pigs (P1, P2, P5, P48) a two-way crossover of fasted and fed administration of the SmartPill® was obtained.

2.4. Study protocol

The study was carried out under the licence issued by the Health Products Regulatory Authority (HPRA), Ireland, as directed by the Cruelty to Animals Act, Ireland and EU Statutory Instruments (Licence number AE19130/P058). Local University ethical committee approval was obtained.

A two-way, cross-over study was conducted in four landrace pigs, a two-week period was used between each group. The SmartPill® was administered together with 50 mL of water. In the fasted arm of the study, the final feed of 175 g of pellet food was given 24 h prior to dosing. The design of the study was to remove any uneaten food 16 hours before the administration of the SmartPill. At this time, however, no food residue remained in any of the groups. In the fed state, pigs were fed half a portion of a standard high-caloric, high-fat FDA breakfast (444 kcal, 315 g). The mass of the FDA breakfast fed equated to approximately 18 – 20 g/kg of body weight. For fed state conditions, the pigs received the meal 30 min prior to oral dosing of the SmartPill®. After dosing, pigs were returned to their pens. All pigs were fed 175 g of pig feed 8 h post dosing (pig weanling food which was considered a normal or 'standard' feed for landrace pigs of this size – equivalent to 20 % protein, 6.5 % oil, 3.5 % fibre or 987 kcal in total). Water was restrained for 3 h post dosing. In Fig. 1, the study of fasted and fed conditions is visually summarized.

3. Results

Overall whole gut transit time (WGTT) was successfully determined using SmartPill® capsules in four landrace pigs (P1, P2, P5, P48) in a two-way crossover of fasted and fed state. The fasted and fed study conditions were based on previous established study protocols, utilizing a standard high-caloric, high-fat FDA breakfast (Henze et al., 2019). Individual profiles of SmartPill® data obtained are illustrated in Fig. 2. As explained in the methods, in three pigs (P3, P6 & P44) the SmartPill® capsule remained in the stomach for more than a week until the battery was completely discharged. They were therefore excluded from the study.

3.1. Transit times

The transit times of the SmartPill® under fasted and fed state conditions are summarized in Table 2. Gastric emptying time (GET) under fasted conditions ranged from 68 –233 h in the four pigs (P1, P2, P5,

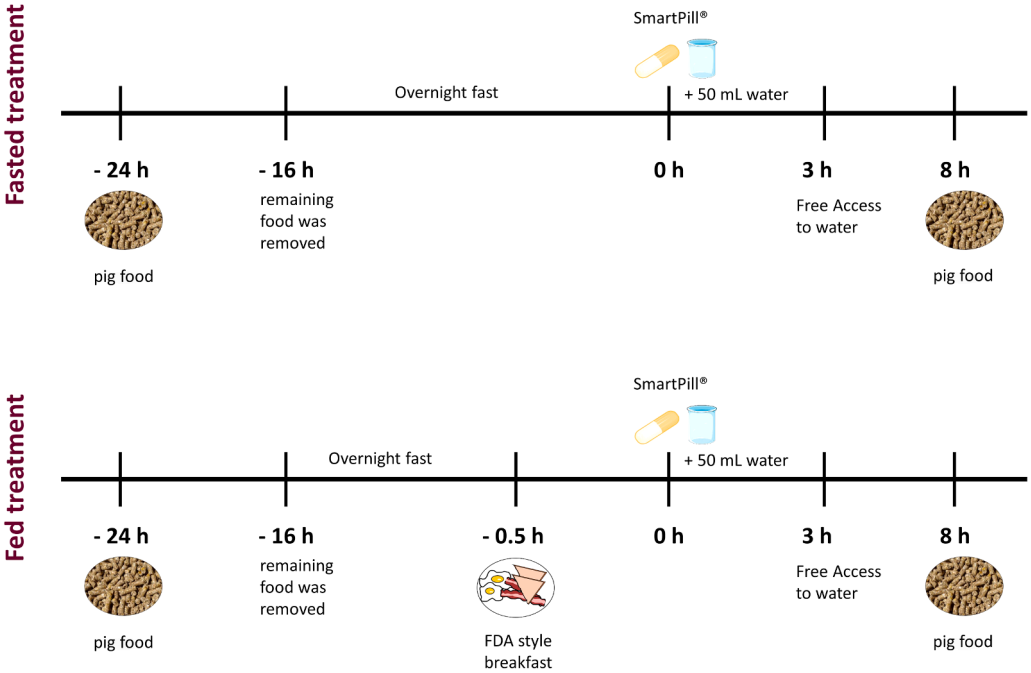


Fig. 1. Study protocol, illustrated a summary of conditions for fasted and fed treatments.

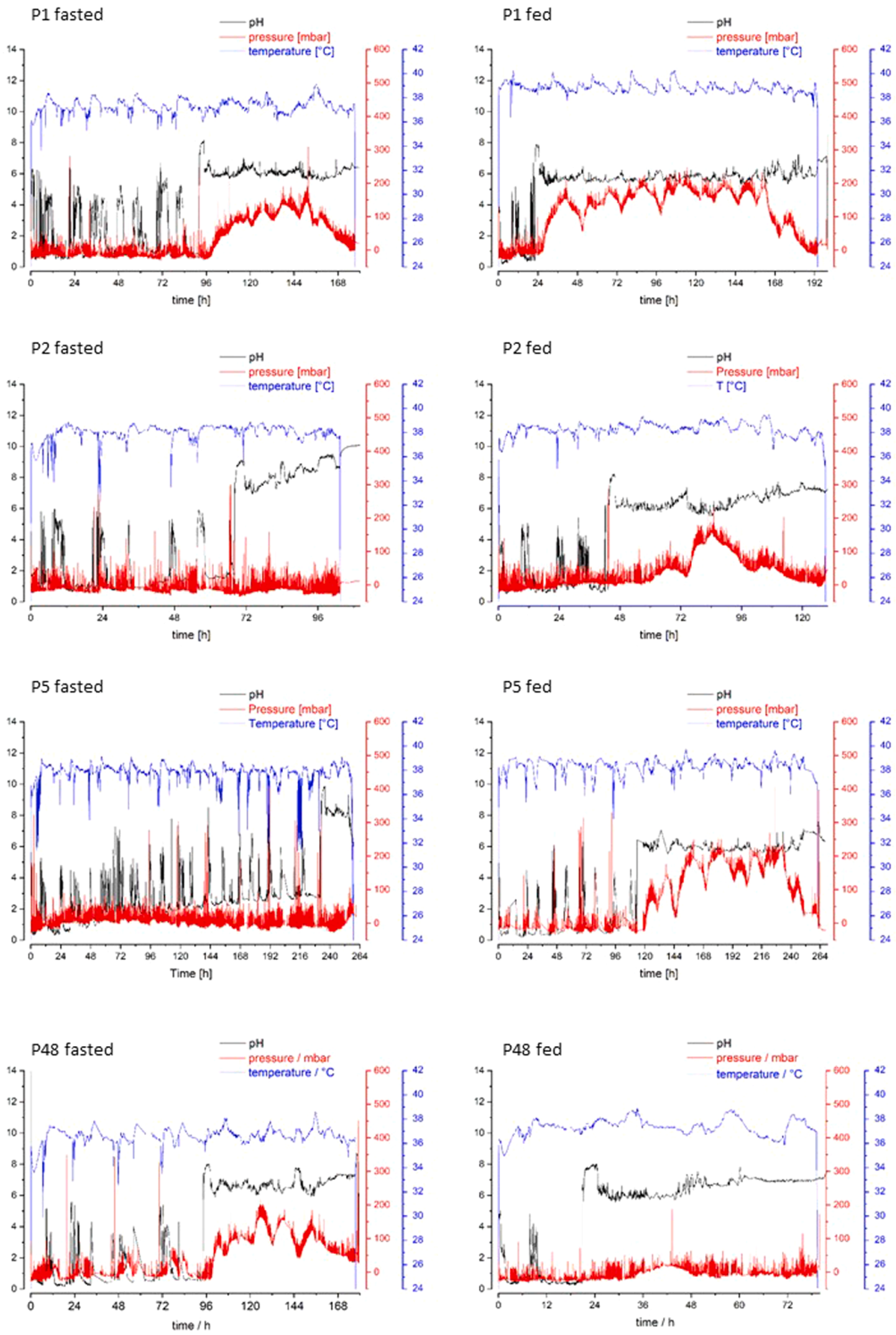


Fig. 2. Individual profiles of SmartPill® data obtained in four landrace pigs (P1, 2, 5, 48) after fasted and (left) fed administration (right).

P48) that completed the study. In addition, two fasted pigs (P3 and P44) displayed a GET of >168 h (P3) and >240 h (P44), as the SmartPill® remained in the stomach. In the fed state GET ranged from 20 –118 h in four pigs, while for one additional pig GET was >264 h (P6) as the SmartPill® remained in the stomach. Consistently in each individual pig a lower GET in the fed state compared to GET in the fasted state was observed. On average GET_{fed} was 3.1-fold lower compared to GET_{fasted}. Small intestinal transit time was not affected by the prandial state, ranging from 2.3 - 4.0 h. The observed colonic transit time in the fasted state was relatively short in comparison to the fed state. Overall, no differences in the whole gut transit time was found between the dosing in the fasted and fed state conditions.

Table 2
Individual transit times of the SmartPill® administered in four male landrace pigs under fasted and fed conditions. GET – gastric emptying time; CAT – colonic arrival time; SITT – small intestinal transit time; CTT- Colon transit time; WGTT – whole gut transit time.

Pig	GET		SITT		CAT		CTT		WGTT	
	fasted	fed	fasted	fed	fasted	fed	fasted	fed	fasted	fed
1	92 h	22 h	2.6 h	2.3 h	95 h	25 h	83 h	169 h	177 h	194 h
2	68 h	43.4 h	3.2 h	2.6 h	71 h	46 h	32 h	83 h	103 h	129 h
5	233 h	118 h	3.2 h	n.a. *	235 h	n.a. *	21 h	> 140 h *	257 h	262 h
48	94 h	20 h	4.0 h	3.8 h	98 h	24 h	79 h	55 h	177 h	79 h

* Signal loss

3.2. pH values

The pH profiles are illustrated in Fig. 3 for fasted and fed state conditions. In the fasted state, for two pigs a general consistent low pH was observed throughout the sampling time, whereas in P5 the pH was higher (~ pH 4) for up to 1 h post administration and in the case of P1, the gastric pH was around pH 6 in the first 2 h post administration. Variability was confined to the first 1 - 2 h for both conditions. The short intervals of pH spikes under fasted condition beyond 3 h may have correlated with drinking water access, as pigs were allowed free access to water 3 h post dosing. In the fed state, elevated pH up to pH 8 were observed initially, which returned to basal acidic levels 2 h post dose. After the initial 2 h the pH was consistently lower. The minimum pH values ranged from pH 0.2 – 0.6 under fasted conditions and fed conditions.

An overview of the individual pH profiles in the porcine small intestine can be seen in Fig. 4. Given that the time to enter the small intestine regions was >20 h, and pigs were fed 8 h post dosing regular pig food in both study arms, from here on we cannot truly define fasted and fed profiles. In the intestinal regions, the pH values ranged from pH 6.2 – 7.5 during the first hour. At the end of the small intestinal transit the pH values were slightly in the range of pH 7.6 - 8.0. The pH values detected in the colon of landrace pigs were equal under fasted and fed conditions (Fig. 5), with a range of pH 5.2 – 7.8.

3.3. Pressures

The maximum pressures detected in the stomach in landrace pigs are illustrated in Fig. 6. The maximum pressure in the stomach compartment were higher compared to the observed data in the small intestine. Furthermore, the maximum pressures in the fed stomach were more variable and slightly lower compared to the fasted state. The maximum pressures in the small intestine were in the same range (< 100 mbar) for fasted and fed conditions (data not shown).

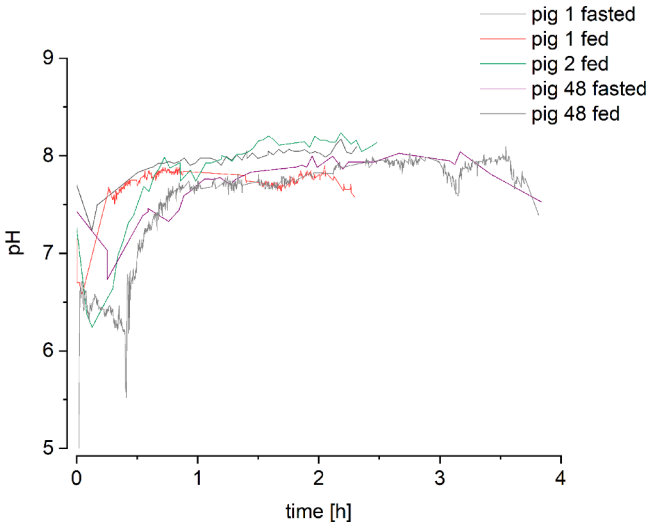


Fig. 4. Comparison of individual small intestinal pH ranges after administration of the SmartPill® in male landrace pigs under fasted and fed conditions (pig 5 no fed state data due to signal loss); Pigs, for whom post-calibration was not possible are not included in the figure (pig 2 fasted, pig 5 fasted).

4. Discussion

4.1. Transit times

In this study, the GI transit times of the SmartPill® were successfully determined in a cross-over design in four male landrace pigs in fasted and fed state. Overall, WGTT obtained with the SmartPill® was similar between fasted and fed state conditions of the four pigs. The transit times through the porcine small intestine were much more consistent than for the gastric compartment. SITT range between 2.3 - 4.0 h, these values

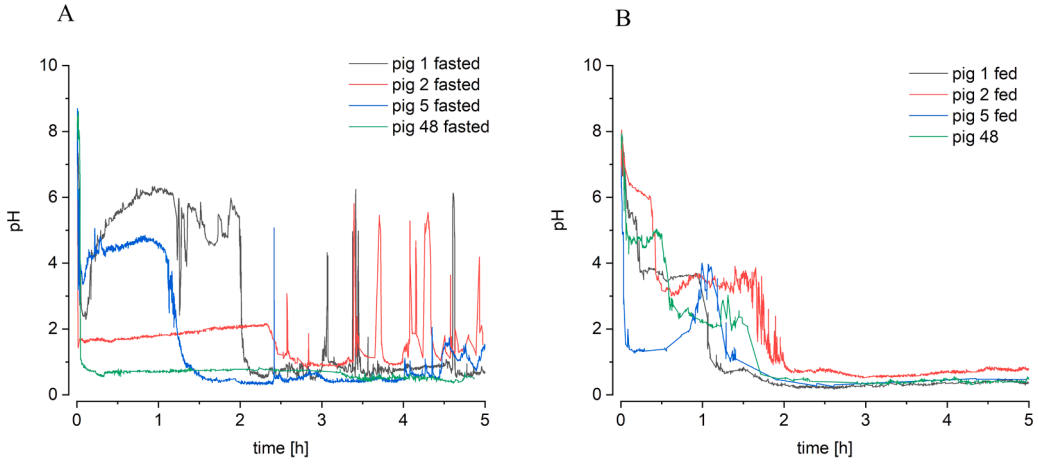


Fig. 3. Comparison of individual gastric pH over the first 5 h after administration of the SmartPill® in male landrace pigs- fasted state (A), fed state (B), n= 4

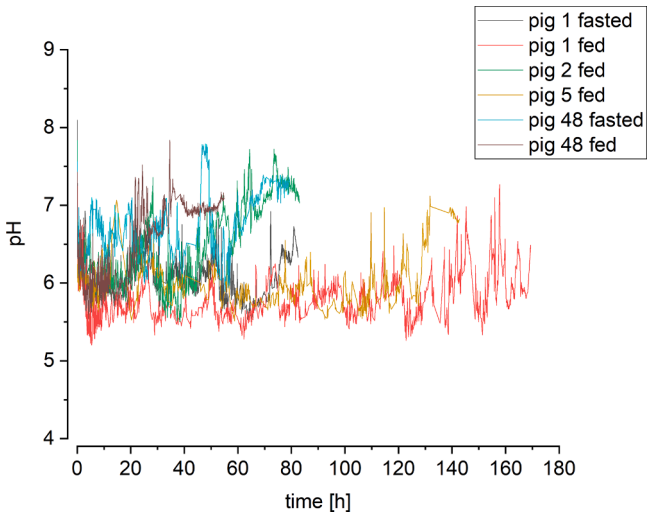


Fig. 5. Comparison of individual colonic pH ranges after administration of the SmartPill® in male landrace pigs. Pigs, for whom post-calibration was not possible are not included in the figure (pig 2 fasted, pig 5 fasted).

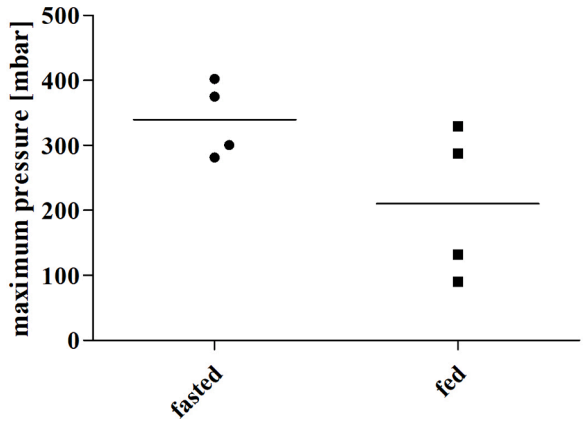


Fig. 6. Maximum pressures in stomach under fasted and fed conditions measured in landrace pigs (n = 4, line indicates the mean)

were in good agreement with reported SITT in humans (3 - 5 h) (Koziolek et al., 2015). The mean colonic transit time in this study was highly variable (Table 2) and overall no significant differences could be observed between fasted and fed pigs. The high variability was in line with previously reported colonic transit times measured by roentgenography in fasted pigs, which ranged between 48 – 792 h (Davis et al., 2001).

For additional three pigs, the capsule remained in the stomach until the battery was completely empty, individual SmartPill® profiles are provided in Fig. S1 (supplementary data). The study confirms that GET for non-disintegrating dosage forms is extremely variable in pigs. While Hossain and co-workers used a different technique, the same effect for non-disintegrating dosage forms was observed. Hossain *et al.* investigated the gastric emptying of a variety of different non-disintegrating dosage forms in pigs by roentgenography and reported gastric transit time of more than 120 h in some cases (Hossain et al., 1990). For instance, large-size plastic tablets (20 mm x 8 mm) had gastric emptying times of 24 – 672 h. However, this study was limited and only included two pigs that were repeatedly dosed for a prolonged period.

In our study, *post mortem* investigations revealed that the capsule was still in the stomach of the three pigs after more than 168 h, 240 h and 264 h, respectively. This phenomenon had already been described in the literature for Göttingen minipigs (Suenderhauf and Parrott, 2013) and Yucatan minipigs (Oberle and Das, 1994), were the telemetric device was recovered from the stomach. During necropsy, the SmartPill® was recovered from the area of the *Torus pyloricus*. This area is a protuberance consisting of fat and muscle fibres, which lies in the muscle-free gap of the sphincter. The pylorus in pigs is relatively stenotic, and thus difficult to overcome for large dosage forms (Suenderhauf and Parrott, 2013). Furthermore, the porcine stomach is "U-shaped", in contrast to the "J-shaped" stomach of humans, which can additionally hamper the emptying of large non disintegrated dosage forms. During stomach contractions, the dosage form would have to be forced upwards toward the pylorus in pigs and the contractions tended to narrow this region, which may further result in prolonged retention (supporting material, video). This phenomenon also explains why in both prandial states very long gastric transit times have been observed, which were clearly longer than gastric transit times of SmartPill® reported in recent studies in dogs and humans (Koziolek et al., 2019; Koziolek et al., 2015). Such long gastric transit times have also previously been reported in pig studies (Davis et al., 2001; Oberle and Das, 1994).

The reasons for the particularly long and variable gastric transit times in this study remained unclear, but may be related to the characteristics of the Migrating Motor Complex (MMC) in pigs. This motility pattern is present only in the fasted state and is interrupted and replaced by fed state motility pattern upon feeding. The MMC can be described by a sequence of three phases of different lengths and intensity. In humans, the emptying of large, non-disintegrating dosage forms occurs primarily during phase III of the MMC. Due to species-specific features of GI tract, differences in cycle and phase duration exist. In pigs, the MMC arrival is related to the feeding frequency and shows a slightly faster motor activity. MMC cycle has a length of 75-80 min in pigs and about 90 – 150 min in humans (Romanski, 2009). Oberle *et al.* suggested that although the fasted MMC in pigs resembles that in humans, the mechanism of gastric emptying of large objects appears to be unrelated to phasic activities in pigs (Oberle and Das, 1994). Table 3 provides an overview of studies reported in the literature using non-disintegrated dosage forms to detect GI transit. Overall, long GET has been reported across four different species of pigs, and GET does not appear to be related to the size of the device relative to the size of the pigs. For example, Suenderhauf *et al.* used the Bravo pH system (6 × 5.5 × 25 mm) in Göttingen minipigs (~ 15 kg), and observed that the capsules stayed at least 48 h in the stomach (Suenderhauf and Parrott, 2013). Whereas, Oberle and co-workers used the Heidelberg capsule (7 mm diameter, 20 mm long) in Yucatan minipig (19 - 40 kg), the capsule was not emptied form the stomach for at least 54 h in one specific case (Oberle and Das, 1994). Hossain *et al.* suggested that the motor activity in pigs might be less efficient in emptying large indigestible dosage forms from the stomach in comparison to humans or dogs (Hossain et al., 1990). However, the maximum pressures that have been observed in this study were in the

Table 3
Overview of gastrointestinal studies conducted in pigs in comparison to this study in Landrace pigs.

Different gastrointestinal studies conducted in pigs					Ref.
Breed	*Body Weight*	*Size of the dosage form*	*Gastric emptying [h]*	*Subject number*	
Landrace pigs	15 -17 kg	26 × 13 mm	68 – 233 h	4	
Yorkshire pigs	45 kg	20 mm x 8 mm	24 – 672 h	2	[1]
Yucatan minipigs	19 – 40 kg	7mm x 20 mm	> 54 h	3	[2]
Göttingen minipigs	~ 15 kg	6 × 5.5 × 25 mm	> 48 h	*	[3]

[1] :(Hossain et al., 1990);
[2] :(Oberle and Das, 1994);
[3] : (Suenderhauf and Parrott, 2013);
* Not reported

same range as reported for humans (Koziolek et al., 2015; Schneider et al., 2016). Therefore, another hypothesis could be that the smaller diameter of the pylorus of the pigs may prevent or hamper the gastric emptying of ingestible objects, in the present study the dosed SmartPills.

Gastric emptying of the SmartPill® was mainly observed in the morning, usually around 6 – 8 am. Hence, the time between the last feeding step in the late afternoon and gastric emptying was 13.6 ± 1.1 h. Table 4 presents a summary of last feeding and gastric emptying of the non-disintegrated capsule. By comparison, a recent published study in humans reported that gastric emptying of SmartPill® after fed administration also occurred mainly at night, with a last meal intake 7.8 ± 2.3 h before gastric emptying of the SmartPill®.

With respect to the effect of food intake on gastric emptying, it can be stated that food did not significantly delay the GET of the SmartPill® in this study when compared to the fasted state. This observation was in contrast to recent data in human and beagle dogs (Koziolek et al., 2019). The mean gastric emptying in the fed state was around 50 h in landrace pigs, however, the data between the pigs was highly variable ranging from 20 - 118 h. Nevertheless, consistently in each individual pig a lower GET in the fed versus the fasted state was observed (Table 2). On average GET_{fed} was 3.1-fold lower compared to GET_{fasted} in each pig. In certain pigs, due to anatomical or physiological aspects, an exceptional long GET was evident under both conditions, this seems to be pig specific. For example, for P5 a very long GET was evident under fasted (230 h) and fed (118 h) state conditions (Table 2), whether this reflected the size of the tours pyloricus or other aspects influenced gastric transit was not clear. Overall, it seemed that gastric emptying time in the fed state was not affected in the same way by the anatomical properties of the pig stomach as under fasted conditions.

4.2. pH values

The fasted gastric pH profiles initially ranged from pH 2.0 to pH 7.0, but dropped to highly acidic pH values of approximately pH 1.8 after the first 2 h. The obtained gastric profiles in fasted landrace pigs showed a high intra-individual variability. Fluctuations in gastric pH profiles can occur due to the dynamic deposition behaviour of the capsule (i.e., when the capsule come in contact with mucosa and then moves away again). This effect may lead to the observed high variability of the measured initial pH. The data in this study corresponded well with existing literature investigating the GI conditions in pigs (Hossain et al., 1990; Oberle and Das, 1994; Suenderhauf and Parrott, 2013). In addition, these values were closely in line with recently published pH values from GI fluid samples, collected *post mortem* in landrace pigs, where a similar range of pH 1.7 – 3.4 was found under fasted conditions. It should also be noted, when using a telemetric capsule a discrepancy in pH values may exist initially when compared to samples collected *post-mortem*, as the capsule was administrated together with 50 mL of water, which may influence the gastric pH values (Koziolek et al., 2019). Nevertheless, these findings confirm that the SmartPill® GI monitoring system is suitable to obtain realistic pH data in a minimally intrusive fashion (Fuchs and Dressman, 2014). In the present work, the pH decreased in the fed state within 2 h to strongly acidic baseline levels (Fig. 3). The feeding 30 min prior to TMC intake stimulated gastric acid secretion, which may cause a fast drop of pH due to the strongly acidic character of the gastric section.

The pH difference between the stomach and the proximal small intestine may play a role in a pH-dependent absorption, but moreover it is very important for the evaluation of precipitation of poorly water-soluble drugs with a weakly basic character. The fasted small intestinal pH determined in this study ranged from pH 6.7 – 7.5 in the duodenum and pH 7.6 – 8.0 in the ileum. These values were comparable to intestinal landrace pig data sampled under *post mortem* conditions (pH 6.3 – 7.9). While on one hand, pH can be measured directly in the GI tract using telemetric systems, *post mortem* examination of intestinal fluids are an alternative approach. However, sampling under *post mortem* conditions may influence the measured pH, whereas the usage of a telemetric capsule can detect a more dynamic pH profile along the GI tract, while this may better resemble the pH an administered dosage form is exposed upon intake.

In most of the pigs, a strong duodenogastric reflux was observed. Short durations with higher pH values could be observed 3 h prior to gastric emptying. An example is illustrated in Fig. 7. Based on the observed data a correlation of pH increase and a distinct high pressure was seen in the fasted state (Fig. 7 A), indicating that the reflux may be associated with intensive motility pattern (MMC phase III). However, in the fed state the strong pressure events were not related to the pH increase, the MMC was probably interrupted and replaced by continuous, medium intensity kind of, contractions upon feeding. The observation that a strong reflux occurred in pigs, was further support by a recently published study in landrace pigs, where high levels of bile acid concentration could be observed in the gastric compartment (2.5 mM) which was 8-fold higher compared to reported gastric bile levels of humans (Henze et al., 2020a). Nonetheless, reflux from the intestine into the stomach, is also a common physiological phenomenon in humans (Castedal et al., 2000; Koziolek et al., 2015).

4.3. Pressures

Insights into pressure patterns as well as the intensity of pressures in the GI tract are of great interest, as for some formulations, drug release can be affected by physiological pressure events. In particular, the drug release from hydrogel matrix tablets, one of the most common approaches for extended release formulations, can be influenced by the pressures occurring in the stomach. The maximum pressures observed in landrace pigs 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. The data obtained in fasted pigs were generally higher than the data from the fed animals, which may be related to the intense peristaltic waves (MMC Phase III) in the stomach. On transfer into the small intestine the intestinal pressures were significantly lower, with the highest pressure measured in the intestine of 99 mbar.

4.4. Comparison of porcine GI transit data with data from dogs and humans

A final objective of this study was to perform a comparison of the GI transit times between landrace pigs, beagle dogs and humans, as presented in Table 5. With respect to gastric transit times in humans, the GET obtained in landrace pigs was longer, it may correlate to the distinctive anatomical characteristics of the porcine stomach as was already outlined above, whereas GET obtained in beagle dogs has been reported to be much shorter (Koziolek et al., 2019). One possible explanation of the variation between the species might be the study protocol and more specifically, the meal composition. Table S1 (supplementary data) summarizes the study conditions from landrace pigs, beagle dogs and humans. While in all of the three studies a similar type of food, containing eggs, toast, milk *etc*. had been used, the amount of kcal per bodyweight varied. In the reported human study, a high-caloric, high-fat standard meal (FDA breakfast) was used for postprandial

Table 4
Relation of the time when gastric emptying (GE) of the SmartPill® occurred, to the last meal intake before GE.

Pig	Fasted		Fed $_{FDA\ breakfast}$	
	GE daytime [hh:mm]	*Last meal intake before GE [h]*	*GE daytime [hh:mm]*	*Last meal intake before GE [h]*
1	05:39	12.49	08:25	14.27
2	06:03	12.70	06:17	12.28
5	03:17	14.78	06:25	13.56
48	07:40	13.42	06:22	12.78

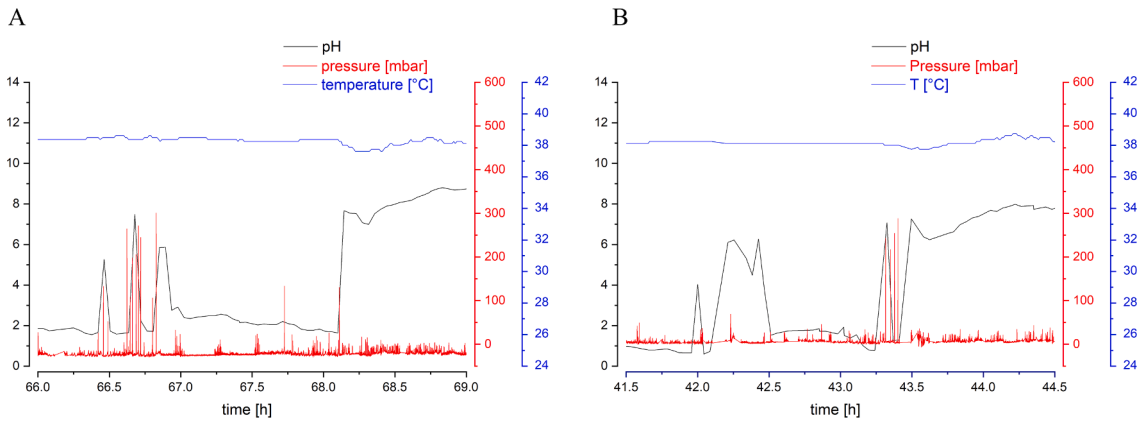


Fig. 7. Gastric profile 3 h prior to gastric emptying, example of P2, on the left-hand side (fasted) and right-hand side (fed).

conditions. This test meal is recommended by FDA and EMA for human food effect studies and contains 965 kcal, which translate into a 13.8 kcal/kg bodyweight ratio (Koziolek et al., 2015). In this study with landrace pigs, a test meal of 444 kcal (half portion of the FDA breakfast) was used, which was based on a recent finding that for food effect studies conducted in landrace pigs a higher caloric FDA breakfast is necessary (Henze et al., 2019). This translates into a 26.1 kcal/kg bodyweight ratio. In a recent study with beagle dogs, the fed state was simulated by administration of a modified FDA meal of ~ 11.3 kcal/kg bodyweight (Koziolek et al., 2019). The meal intake after dosing is also different for the reported studies. While in studies conducted in humans, lunch was provided 4.5 h after ingestion of the SmartPill®, beagle dogs got standard dog food 4 h after SmartPill® administration. In this study, landrace pigs got pig standard weaning food 8 h after SmartPill® administration. All in all, it can be summarized that the high-caloric density of the food and deviations in the study protocols, in terms of meal intake prior and post dosing, may have influenced gastric transit conditions. However, there are also differences between the species that are not completely defined by the food protocol, that may have led to GET differences across the species.

The transit times through the porcine small intestine were similar to human conditions, whereas in contrast dogs display a shorter SITT of 1 – 2 h (Table 5). It has been suggested that the shorter intestinal transit times can be correlated to different dimensions of the small intestine. In dogs, the small intestine appears to be shorter compared to humans and pigs (Koziolek et al., 2019). The small intestinal physiology is generally comparable between pigs and humans, which is considered favourably in the context of similarity of the drug absorption process for both (Henze et al., 2018b). Overall, this study further supports these findings, in that the transit in the primary absorptive region of the GI tract was broadly similar, further supporting the suitability of the pig model to evaluate the kinetics of drug absorption of immediate release dosage forms.

In pigs, mean colonic transit times are in general longer in comparison to humans, but also very variable (Koziolek et al., 2015; Schneider et al., 2016). In dogs the average colonic transit time was reported to be slightly higher in comparison to human colonic transit times (Koziolek et al., 2019). Colonic transit times are important when evaluating extended release (ER) formulations, and it is critical that allowances are made for the generally longer colonic residence times of non-disintegrating dosage forms observed in pigs and dogs, when extrapolating to humans. Overall these findings would suggest that for sustained release monolithic dosage forms that the potential window for drug release is likely to be exaggerated in dogs, and even more so in pigs.

By comparing the present data set in landrace pigs to recently published studies in humans, it can be seen that gastric pH observed under fasted and fed conditions was in the range of humans (Fig. 8). In contrast, it has been shown that dogs have an elevated gastric pH, which could lead to issues when evaluating enteric coated formulation and their potential *in vivo* performance, which can be overcome by pentagastrin administration (Koziolek et al., 2019).

In comparison to human fasted intestinal conditions, duodenum pH 5.3 – 6.4 (median pH 5.9), ileum pH 6.8 – 7.6 (median 7.5) (Schneider et al., 2016), the data observed in landrace pigs was marginally higher, although the typically pH increase from the proximal to the distal parts of the intestine can be seen for both humans and pigs (Fig. 9). In comparison to the observed data in pigs, dogs have a similar pH, recently published, canine intestinal pH data, revealed that dogs also show a higher pH when compared to humans (Koziolek et al., 2019).

The colonic pH values in pigs and humans were in the same range (range: 5.2– 7.8), as illustrated in Fig. 10. A similar pH range has been reported for dogs (pH 5.0 – 8.0). Nonetheless, colonic pH values are variable, Koziolek and co-workers hypothesized that observed changes in pH values indicate transit through the colon, whereas constant pH values might be a sign that the telemetric capsule stayed at a certain region within faecal contents. In dogs, relatively long durations of constant pH have been measured in the colon, a similar effect can be observed in pigs in the present study.

In humans, high pressure activity has been reported in the stomach with maximum pressures up to 500 mbar (Koziolek et al., 2015; Schneider et al., 2016). In comparison to reported human data, the data obtained in this study showed that the pigs displayed similar maximal pressure values (402 mbar), and were closer in mimicking human

Table 5
Transit times of the SmartPill® administered in four male landrace pigs under fasted and fed conditions (mean ± SD, n=4), compared to published literature of humans and beagle dogs; GET – gastric emptying time; CAT – colonic arrival time; SITT – small intestinal transit time; CTT- Colon transit time; WGTT – whole gut transit time.

	Landrace pigs		Humans		Beagle dog [c]	
	Fasted	*Fed $_{FDA\ breakfast}$* [1]	*Fasted*	*Fed $_{FDA\ breakfast}$* [2]	*Fasted*	*Fed $_{FDA\ breakfast}$* [3]
GET [h]	121.80 ± 74.91	50.51 ± 44.93	0.83 ± 1.08 [a]	15.33 ± 4.65 [b]	0.57 ± 0.37	2.94 ± 0.91
SITT [h]	3.46 ± 0.48	2.91 ± 0.81	4.45 ± 0.68 [a]	4.94 ± 1.72 [b]	1.37 ± 0.59	1.94 ± 0.27
CTT [h]	53.77 ± 31.68	102.47 ± 59.54	12.44 ± 8.70 [a]	15.60 ± 12.23 [b]	25.4 ± 3.3	28.2 ± 4.7
WGTT [h]	178.83 ± 62.86	165.94 ± 79.16	17.70 ± 8.91 [a]	35.87 ± 10.6 [b]	27.3 ± 3.3	33.0 ± 4.1

[1] 444 kcal
[2] 965 kcal = 13.8 kcal/ kg bodyweight
[3] 150-200 = 11.3 kcal/kg bodyweight = homogenized meal
[a] (Schneider et al., 2016)
[b] (Koziolek et al., 2015)
[c] (Koziolek et al., 2019)

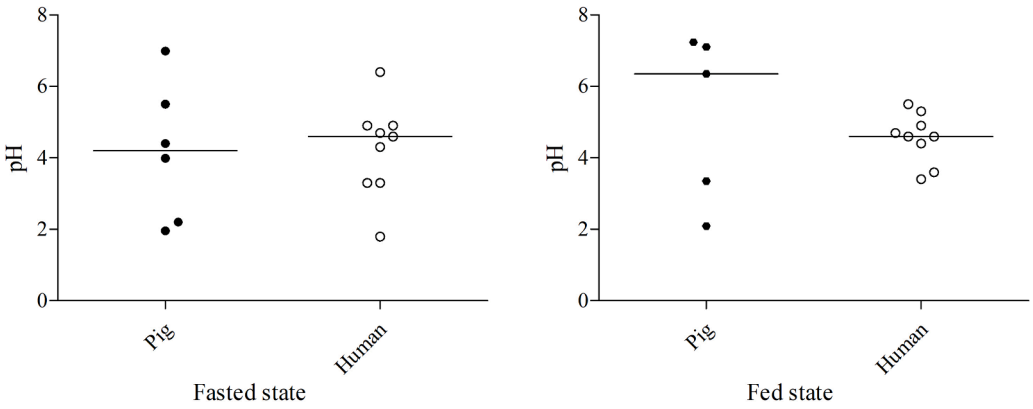


Fig. 8. Comparison of initial individual gastric pH values observed in landrace pigs (n=5,6) and humans (n=9) (Schneider et al., 2016) after fasted and fed state administration of the SmartPill® (line is indicating median).

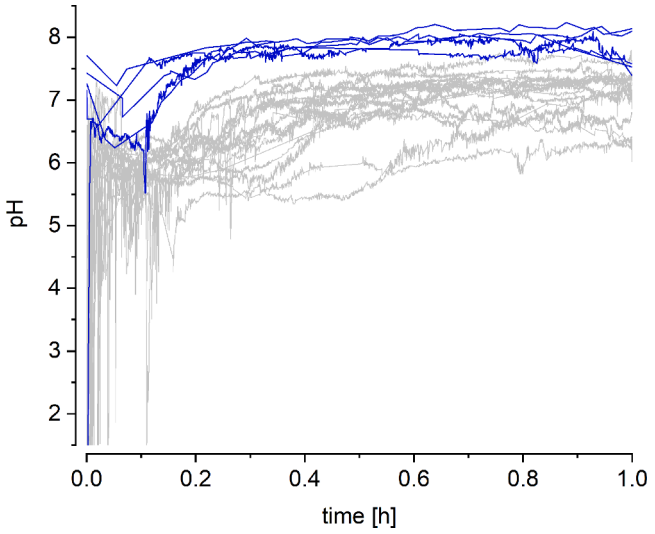


Fig. 9. Comparison of small intestinal pH values observed in landrace pigs (blue n= 4) and humans (grey, n= 19) after administration of the SmartPill®. Human data were published recently by Koziolek and co-workers (Koziolek et al., 2019).

stomach conditions than dogs. In beagle dogs, gastric maximum pressures of 800 mbar have been reported, which was significantly higher than the reported human values (Koziolek et al., 2019). Koziolek and co-workers emphasized that dogs could still be a useful species to evaluate modified release formulations as a worst-case scenario in terms of mechanical stress occurring in the GI tract. Higher pressures in the stomach may result in unexpected drug release scenarios; such as dose dumping. This is suggested to make the dog model attractive and useful to assess the uncertainty of dose dumping of extended release formulations under conditions of elevated gastric pressure. Nevertheless, the pig model may offer the advantage for general pharmacokinetic studies to represent more human like conditions in terms of pressure activity in the stomach. The pressures during small intestinal passage were 60 ± 35 mbar in humans, which was comparable to the observed pig data. The intestinal maximum pressure measured in beagle dogs is approximately 200 mbar, reflecting a 3.3-fold increase compared to humans and pigs.

4.5. *The pig as a preclinical model within drug formulation development*

While it is commonly recognised that there is no 'ideal' species that represent all aspects of human GI conditions, favourable correlations between pig and human bioavailability values have generally been supportive of the suitability of the pig model for gaining first insights into *in vivo* absorption parameters of new drug products (Henze et al., 2018b). However it has been noted that the rate of drug absorption was generally slower in pigs than in humans, resulting in a rule of thumb that reported tmax in pigs were on average 2-fold higher than observed tmax

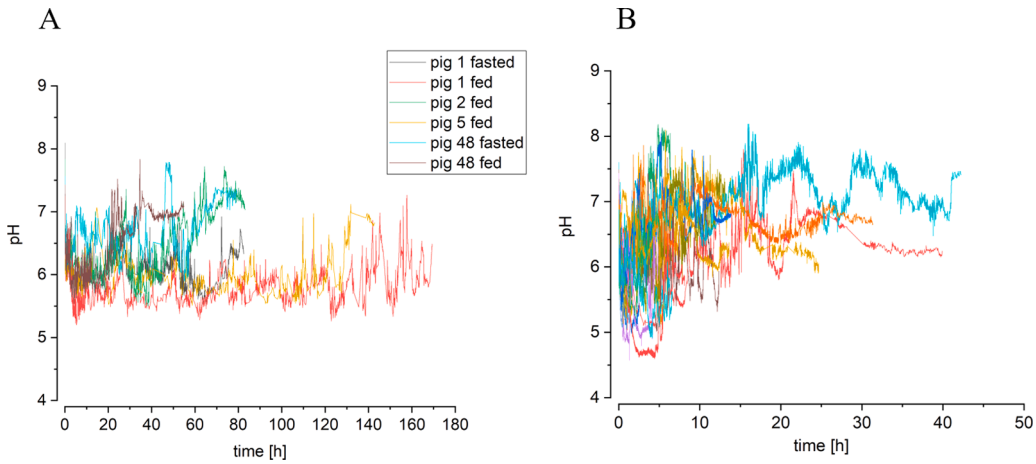


Fig. 10. Comparison of colonic pH values observed in landrace pigs (A, n= 4) and humans (B, n= 19) after administration of the SmartPill®. Human data were published recently by Koziolek and co-workers (Koziolek et al., 2019).

data in humans for the same drug (Henze et al., 2018b). The current study provided additional insights to explain the slower rate of absorption observed for a variety of drugs, reflecting a slower overall clearance from the stomach. Once presented to the intestine, given the similar small intestinal transit time, drug absorption kinetics are likely to be well matched between pigs and humans. In general, this study therefore supports the suitability of the pig model for assessing the absorption kinetics of immediate release oral dosage forms in humans. However, in the case of large non-disintegrating tablets/capsules, the study confirms that such dosage forms are likely to likely to display a variable and extended gastric residence time in pigs, and hence caution is advised when extrapolating absorption kinetics for such monolithic drug products from pigs to humans..

In terms of modified release formulation, the choice of animal model requires careful consideration. For enteric coated formulations, the lower pH in pigs would tend to be a better guide to performance in humans, however, this needs to be balanced with the highly variable GET for non-disintegrating dosage forms. In the case of enteric coated pellets (e.g. 0.9-1.5 mm in diameter) the pig model may still be suitable, as the smaller sized pellets are less likely to be impeded at the *Torus pyloricus* (Davis et al., 2001). In general, for sustained release formulations, where the drug may be intended to be released over an extended period of time, the GET may be a critical parameter in predicting the performance of the formulation in humans. For gastro-retentive dosage forms, the findings in this study also potentially shed new insights on the utility of the pig. While pigs have been used to investigate gastro-retentive devices (Brayden and Baird, 2019; Kirtane et al., 2018), based on the observations with SmartPill® data presented here, it is questionable whether observation in pigs, which most likely reflect the delayed clearance of larger devices from the stomach, will reliably translate to humans. However, in a situation where worst-case evaluation of a modified release dosage form, such as to assesses the risk of dose dumping during prolonged gastric residence, the pig model may therefore be considered a suitable approach.

5. Conclusion

The study showed that the data observed in pigs, using the SmartPill® was closely aligned to reported SmartPill® data in humans. However, the study demonstrated that gastric transit times of non-disintegrated dosage forms was variable and prolonged in pigs, compared to studies conducted in humans. Therefore, while this study supports the suitability of the pig model for evaluation immediate release oral dosage forms, the findings confirm a limitation of the porcine model when used for the evaluation of gastro-retentive and/or large non-disintegrating oral dosage forms, which are likely to display an extended gastric residence time, in pigs. Nonetheless, it was shown that the small intestinal transit conditions in pigs were similar to humans, and detected GI pH values and pressures, were comparable between pigs and humans. The fed state GET in pigs, unusually appeared to be shorten in all pigs comparted to fasted conditions, which was in contrast to reported effects in humans. By comparing the observed SmartPill® data in landrace pigs, with recent data from beagle dogs, it was demonstrated that important differences exist between these pre-clinical species, that should carefully be taken into account when selecting an appropriate model for specific formulation strategies.

CRediT authorship contribution statement

Laura J. Henze: Writing - original draft, Methodology, Conceptualization. **Niklas J. Koehl:** Software, Data curation. **Harriet Bennett-Lenane:** Software, Data curation. **René Holm:** Supervision. **Michael Grimm:** Software, Visualization. **Felix Schneider:** Software, Visualization. **Werner Weitschies:** Supervision. **Mirko Koziolek:** Software, Visualization, Supervision. **Brendan T. Griffin:** Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2020.105627.

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