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Research Paper

Interplay Between Intestinal pH, Transit Time and Feed Status on the *In Vivo* Performance of pH Responsive Ileo-Colonic Release Systems

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Purpose. Oral pH triggered drug delivery systems, for targeting to the lower gastrointestinal tract, show erratic behaviour *in vivo*. This study aimed to establish correlations between *in situ* gastrointestinal pH, transit time or feed status and the disintegration of pH-responsive dosage forms designed to dissolve above pH 7.
Methods. Tablets (radiolabelled with Technetium 99m) coated with Eudragit S were administered to eight healthy subjects in a three-way crossover study after an overnight fast. Food was administered either 30 min after (pre-feed) or 4 h after (fasted) tablet ingestion. Concurrently, a Bravo® pH monitoring capsule (radiolabelled with Indium 111) was administered in a "freefall manner". In a third arm of the study tablets were given immediately after breakfast (fed). Transit was followed by gamma scintigraphy.
Results. Gastrointestinal pH showed variability between and within individuals but no differences were seen between pre-feed and fasted states. Three tablets failed to disintegrate in pre-feed and fed regimens and one in the fasted state; this has been tentatively linked to ileocaecal pH and ileoceacal junction residence time.
Conclusions. *In vivo* performance of "pH-responsive" dosage forms is complex and influenced by a multitude of factors other than just *in situ* pH.

KEY WORDS: colonic delivery; enteric coating; inflammatory bowel disease; polymethacrylic acid methyl methacrylate ester copolymer; radiotelemetry.

INTRODUCTION

The colon serves as an important site for oral drug delivery, principally for the local treatment of pathologies such as inflammatory bowel disease. One of several proposed strategies for targeting the colon is the exploitation of pH changes along the gastrointestinal tract and a number of preparations are commercially available (1). The pH sensitive polymers utilised for lower bowel targeting are insoluble in the low pH of the proximal gut and dissolve at the higher, near neutral pH of the distal gut. The pH has been measured to be 1–2.5 in the stomach increasing through 6.6±0.5 in the proximal small intestine to a maximum of 7.5±0.4 in the distal small intestine (2). Eudragit S (a polymethacrylic acid methyl methacrylate ester copolymer), with a dissolution threshold of pH 7, is commonly applied as a coating on solid dosage forms to target the colon (3). It was first used by Dew *et al.* (4) which led to the development of Asacol® (containing 400 mg of mesalazine for the treatment of ulcerative colitis) and other similar products worldwide. Recently, 800 mg mesalazine products (Asacol® 800) have become available as well as new systems with 1.2 g drug doses [Lialda® (US) and Mesavant® (Europe)]; their release mechanisms are based on the same pH sensitive concept.

Despite the simple concept on which pH sensitive delivery systems are based, there is extensive evidence for their temperamental behaviour *in vivo*. Schroeder *et al.* (5) and Sinha *et al.* (6) have reported Asacol® tablets failing to disintegrate in the gastrointestinal (GI) tract of patients with ulcerative colitis and passing through intact. The compromised drug delivery arising from incomplete tablet disintegration has been illustrated in a study by Safdi (7) on Asacol® tablets. Fragments of tablets were retrieved from volunteers' faeces and assayed; on average they were found to contain 97.2±47.1 mg mesalazine, which is 24% of the 400 mg administered dose.

Other researchers have examined model preparations based on the same pH sensitive polymer (Eudragit S) and noticed similar phenomena in healthy subjects (8,9). For tablets that did disintegrate, however, variability in time and onset of disintegration was demonstrated. It has been speculated that the threshold pH of this polymer may not have been attained in the distal GI tract of these individuals in whom disintegration fails (8). Wilding (10) investigated the effect of food on the behaviour of Asacol® in healthy subjects; the time and site of disintegration was found to vary with feed state however the reason for this was not identified. There is a lack of understanding of the fundamental factors affecting these dosage forms *in situ*. For instance, although the basic *in vitro*

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principle of drug release from the Eudragit S coated system is dissolution of the coating above pH 7, the actual *in vivo* dissolution threshold has not been substantiated. Furthermore, in one quarter of healthy individuals, the pH threshold of Eudragit S is not reached (11) and in a similar proportion of ulcerative colitis patients, a luminal pH>7 was maintained for less than 30 min (12).

The aim of this study was to investigate the relationship between *in situ* gastrointestinal pH and dosage form transit and residence times on the *in vivo* performance of Eudragit S coated polymer systems in healthy individuals. Particular attention was given to the ileocaecal junction residence time as this is the region of the GI tract expected to have the highest pH. Feed status, normally assessed in the fasted (after overnight fast) or fed state (after a standard breakfast) was expanded to provide a broader scope of dosing scenario. This *pre-feed* dose involved breakfast consumption 30 min after taking the dosage form. A radiolabelled pH monitoring system (Bravo® pH capsule) was administered with this pre-feed dose, and with the fasted dose, along with a radiolabelled Eudragit S coated tablet. The transit of each was followed by gamma scintigraphic methods, enabling the *in situ* pH and transit times experienced by the coated tablet to be established.

MATERIALS AND METHODS

Materials

Eudragit S was donated by Evonik (Darmstadt, Germany). Prednisolone Eur. Ph. was obtained from Aventis Pharma SA (Antony, France). Lactose was obtained from Ellis and Everand (Essex, UK). Polyvinyl pyrrolidone was purchased from VWR International Ltd, (Poole, UK). Croscarmellose sodium (Ac-Di-Sol) was a gift from FMC International, Ireland. Bone cement (DeTrey1 Zinc) was given by DentsPly GmbH, Germany. Technetium 99m (^{99m}Tc)—diethylenediaminepentaacetic acid (DTPA) and indium 111 (^{111}In)—DTPA were obtained from Amersham (Hammersmith Hospital, London) and were delivered each morning on the day of the study. The Bravo® pH receivers, calibration buffers, calibration modules, and computer system preinstalled with Polygram Net Software for data processing was provided by Synectics Ltd (Herts., UK). All other materials were obtained from Sigma (Poole, UK).

Preparation and Radiolabelling of Coated Tablet Cores

Tablet cores, designed to rapidly disintegrate, were prepared. These were 8 mm in diameter, with a 200 mg nominal weight. Prednisolone was incorporated as a model drug to validate the radiolabelling procedure and the tablets were prepared by wet granulation (prednisolone 5%, lactose 85%, polyvinyl pyrrolidone 5%, croscarmellose sodium 4% and magnesium stearate 1% [added extragranularly]). The tablets were coated with Eudragit S organic solution as described previously (13). A coating level equivalent to 5% total weight gain was applied, which corresponds to 5.2 mg/cm^2 polymer and 84 μm coating thickness. The Eudragit S coated tablets were radiolabelled with ^{99m}Tc complexed to DTPA, as described by Ibekwe *et al.* (9). Briefly, lactose was dissolved in the radioactive complex and oven dried. A 1 mm diameter hole was drilled into the coated tablet surface into the core and the radiolabelled lactose used to fill the hole, to an activity of 4 MBq and the hole sealed with bone cement. *In vitro* disintegration tests showed that the disintegration of labelled and unlabelled tablets was identical. *In vitro* studies of drug release showed the integrity of the coating not to be compromised by the labelling process and the labelled tablets gave identical drug release profiles as unlabelled tablets in simulated gastrointestinal conditions. The release of the radiolabel mirrored the release of the drug.

Collection of *In Vivo* pH Measurements

In vivo pH measurements were taken using the Bravo® pH system: a novel radiotelemetry pH monitoring system (pH range 0.5–9.0, dimensions 5×6×25 mm, weight 1.50 g). The Bravo® pH capsule has been used previously to establish oesophageal pH in reflux patients (14, 15); in this case the pH capsule is tethered. This investigation represents a novel use of the Bravo® pH capsule, in which "freefall" pH monitoring method is used to measure pH throughout the gastrointestinal tract of man. The pH capsule was swallowed by volunteers and the pH data signals were transmitted to a receiver worn on the patient's waistline, at 6 second intervals. It should be noted that the pH capsule and the Eudragit S coated tablet were not tethered to each other and the pH capsule was radiolabelled to monitor the transit. ^{111}In-DPTA was added to a small quantity of lactose, which was oven dried and pulverised, and the required activity (0.6 MBq) was filled into a well at one end of the pH capsule, which was then sealed with bone cement paste. The Bravo® pH capsule was considered easy to swallow, however volunteer 5 declined from doing so in the pre-feed study.

Study Protocol

The study protocol and radioactivity administration was approved by the Committee on Ethics of Human Research of the East London and City Health Authority and the Administration of Radioactive Substances Advisory Committee (Department of Health). The study followed the tenets of the Declaration of Helsinki (1964). Eight healthy adult male volunteers, aged 22–34, took part in the study, with treatment order randomised and 7-day wash-out periods observed. The volunteers were administered a radiolabelled Eudragit S organic coated tablet, along with the radiolabelled Bravo® pH capsule, after:

1. An overnight fast (fasted)
2. An overnight fast with a standard breakfast 30 min post dose (pre-feed)

Further to this:

3. An Eudragit S coated tablet was ingested immediately after a standard breakfast (fed) without administration of the Bravo® pH capsule

The standard breakfast was composed of 30 g cornflakes, 100 ml semi-skimmed milk, two slices of toasted brown bread, 5 g margarine and 150 ml orange juice. A further volunteer (subject 9) received the radiolabelled pH capsule on two separate occasions in the fasted state to determine intra-subject variability of pH. The tablet and pH capsule were

swallowed with 150 ml of water, and the pH monitoring was commenced upon swallowing. A sealed point source of 0.5 MBq ^{99m}Tc was taped to the most lateral part of the lower costal margin to be used for correction of posture between imaging and as an anatomical reference marker.

Images were acquired using a single head camera (GE Maxicamera 400AC) with energy windows set at 126–150 KeV for ^{99m}Tc and 221–274 KeV for ^{111}In. Images were acquired over a 1-min period, at an average of 10-min intervals, for up to 14 h. The frequency of imaging was increased at times of interest, for example gastric emptying. Volunteers continued to fast until a standard lunch was provided at 4 h post-dose, after which water and other non-alcoholic drinks were freely available. The acquired images for each volunteer were replayed on a computer, and processed using Nucmed software (MicasX, Farnborough, UK). Analysis of the images and derivation of the gastric emptying (GE), ileocaecal junction residence, colonic arrival and tablet disintegration times was performed independently by two investigators one of whom was blinded to the study. Both independent analyses reached similar interpretations. Small intestinal transit time was derived by subtracting the gastric emptying time from the colonic arrival time. This was further sub-divided into upper small intestinal transit time by subtracting the ileocaecal junction residence time from it. Since the images were not continuous, the time of the various events were taken as the mean of the two time points at either side.

Statistics

The effect of pH and the effect of ileocaecal junction residence time (ICJRT) on tablet breakage were assessed using Student's *t* test and Mann–Whitney *U* test. The effect of both pH and ileocaecal junction residence time combined was assessed using multiple regression. Comparisons between fasted, pre-feed and fed states on the transit of Eudragit S tablets were carried out using a one way ANOVA followed by post hoc analysis using Tukey's test. Comparisons between the pre-feed and fasted state on pH and pH-capsule transit were carried out using a Mann–Whitney *U* test. All tests were carried out using SPSS Version 14.0 statistical software. Significance was assumed where $p<0.05$.

RESULTS AND DISCUSSION

In Situ pH Measurements

The Bravo® pH capsule was successfully used to monitor the pH throughout the GI tract, and is the first example of its use in a "free fall" human GI situation. Each administered capsule is single-use only and volunteers were requested to recover the capsule from the faeces where possible. Out of a total of 17 administrations [the eight study subjects on two occasions with one subject declining to swallow the capsule on one occasion, and the further subject (volunteer 9) on two occasions], 12 capsules were recovered. These were washed and checked using calibration buffers to assess pH drift during the study. No capsules drifted by more than 0.2 pH units. This contrasts with the study by Evans *et al.* (2) whereby pH drifts of up to 1 pH unit were observed and these results utilised; this was attained with pH capsules utilising a different technology.

The pH profiles of one subject, in which the capsule was ingested without food (fasted) or after having eaten 30 min post capsule ingestion (pre-feed), are shown in Figs. 1a and b. The individual pH values for each of the eight study volunteers, taken as an average reading at points along the GI tract, are seen in Tables I and II; the pH was measured in the fasted and pre-feed states, but high variability between individuals meant that statistical analysis failed to find any difference between the pH between these feeding states ($p>0.05$). This is in agreement with Kalantzi *et al.* (16), who found that there was no difference in the pH, in the fed and fasted state, of duodenal aspirates from healthy subjects.

The measured pH in the stomach ranged from 0.8–1.8 in the fasted state, to 1.1–3.1 under the pre-feed regimen. In this latter feeding regimen, meal administration led to a transient rise in pH in some subjects due to the buffering effects of food. The pH values measured in the fasting stomach are in agreement with Dressman *et al.* (17) and Russell *et al.* (18), in which a median fasting pH of 1.7 (1.4–2.1) is reported. The same authors report a range of 4.3–5.4 in the fed state. The rise in pH after feeding is thought to be dependent on the type of meal (19) and it is suggested that the light meal ingested was not able to produce a sustained rise in gastric pH. Furthermore, as the capsule was ingested before the food, it may be resting in the curvature of the stomach, and not be mixed with ingested food.

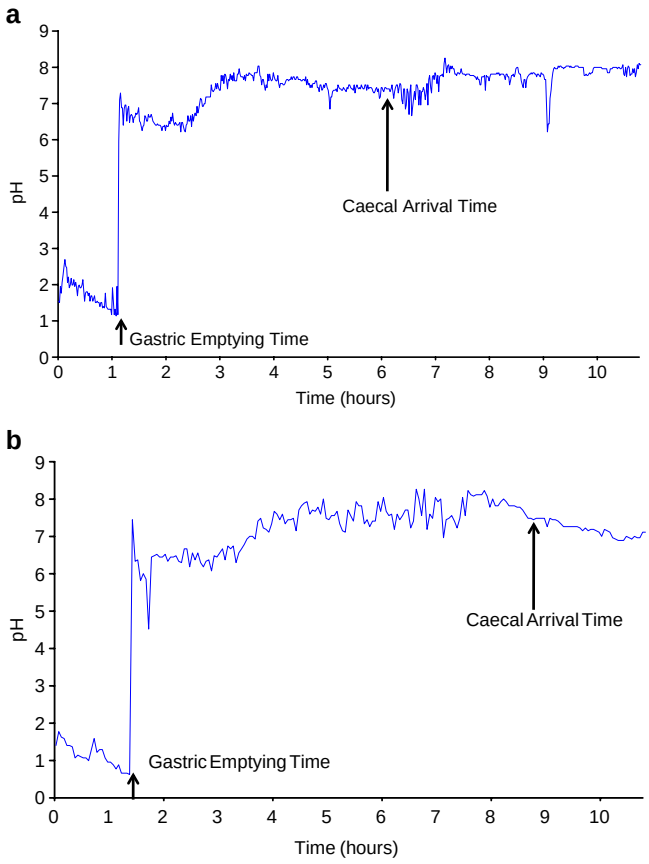

Fig. 1. **a** The gastrointestinal pH profile of subject 1 (fasted); **b** the gastrointestinal pH profile of subject 1 (pre-feed).

Table I. The pH of Individual Subjects (Fasted)

	In Situ pH				
		Upper Small Intestine			
Subject	Stomach	Proximal Small Bowel	Mid Small Bowel	Distal Small Bowel Including Ileocaecal Junction	Ascending Colon
1	1.7±0.3	6.5±0.2	7.3±0.4	7.5±0.1	7.6±0.3
2	1.8±0.3	6.0±0.4	7.0±0.8	7.2±0.1	7.1±0.3
3	0.8±0.3	6.2±0.8	6.7±0.3	7.6±0.2	7.1±0.2
4	1.3±1.2	7.0±0.4	6.3±0.5	7.5±0.2	6.5±0.2
5	1.2±0.1	6.4±0.3	6.8±0.2	7.3±0.3	6.2±0.1
6	1.7±0.9	6.8±0.5	6.7±0.7	6.8±0.3	5.5±0.7
7	1.2±0.2	6.7±0.5	6.7±0.7	7.7±0.2	–[a]
8	1.1±0.2	6.2±1.2	6.7±1.2	6.7±0.9	5.8±0.2
Mean±SD	1.4±0.4	6.5±0.3	6.8±0.3	7.2±0.4	6.5±0.8

[a] Bravo® pH capsule stagnated at the ileocaecal junction and so the pH of the ascending colon could not be ascertained during the imaging period

As the capsule leaves the stomach, there is a sustained steep rise in pH as the capsule enters the more alkaline lumen of the duodenum. This emptying into the small intestine is confirmed by gamma scintigraphy images. The measured pH values in the proximal, mid and distal small intestine are in agreement with those measured previously (2,20,21). From the ileocaecal junction to the caecum, a fall in pH was seen in some subjects, whilst in others the pH remained stable. The drop, where seen, was gradual, and is in contrast with the sharp drop of 1 or more pH units reported by other authors (2,20,22). This gradual drop in pH makes it more difficult to determine arrival of capsules into the caecum and hence gamma scintigraphy is necessary to locate the capsule.

Figure 2 shows two gastrointestinal pH profiles from volunteer 9 on two different occasions in the fasted state, 1 week apart. On both study days, the subject was fasted, and there was no change in diet. From this, the substantial levels of intra-subject variability become apparent; this is expected given the heterogeneity of the *in vivo* environment. This variability is also, in part, due to the transit of the pH capsule whereby it spends variable amounts of time in different regions of the GI tract. Figure 2 illustrates that on the first occasion the capsule has a gastric emptying time of around half an hour, and a small intestinal transit time of 6 h. On the second administration 1 week later, the capsule takes 3 h to empty from the stomach, and 10 h to travel through the small intestine.

In Situ Transit Measurements

The transit times of both the pH capsule, and the Eudragit S coated tablet were monitored to establish if the measured pH at a given point and time was reflective of the pH experienced by the Eudragit S coated tablet. The transit times of the pH capsule, in the pre-feed and fasted state, are shown in Table III, and the transit times of the Eudragit S coated tablets, in the fasted, pre-feed and fed states, are shown in Tables IV, V, and VI. On average, the pH capsule and Eudragit S tablets empty within 20 min of each other in the fasted state, suggesting they are both emptied with the contractions of the migrating myoelectric complex (23,24). With the pre-feed regimen the gastric emptying time tends to be longer for the relatively larger pH capsule, and on average they empty within 1 h of each other. In the small intestine, the transit times of the capsule and tablet in both feeding states are different, and are probably influenced by the size difference of the capsule and tablet. The differences

Table II. The pH of Individual Subjects (Pre-Feed)

	In Situ pH				
		Upper Small Intestine			
Subject	Stomach	Proximal Small Bowel	Mid Small Bowel	Distal Small Bowel Including Ileocaecal Junction	Ascending Colon
1	1.2±0.3	6.3±0.3	7.0±0.5	7.7±0.3	6.8±0.3
2	1.3±0.5	5.9±0.6	6.6±1.6	7.5±0.6	7.1±0.3
3	1.1±0.7	6.2±0.7	6.2±0.8	6.9±0.3	6.8±0.4
4	1.8±0.2	6.6±0.4	7.5±0.2	7.6±0.8	6.4±1.5
5	–[a]	–[a]	–[a]	–[a]	–[a]
6	1.5±0.6	6.3±0.5	6.3±0.4	7.8±0.3	7.6±1.8
7	3.1±1.1	6.2±0.6	6.8±0.2	7.1±0.03	–[b]
8	1.7±0.6	6.4±0.6	6.6±0.4	7.6±0.2	6.6±0.3
Mean±SD	1.6±0.7	6.2±0.2	6.7±0.4	7.4±0.3	6.9±0.4

[a] Subject 5 declined to swallow the Bravo® pH capsule
[b] Bravo® pH capsule stagnated at the ileocaecal junction and so the pH of the ascending colon could not be ascertained during the imaging period

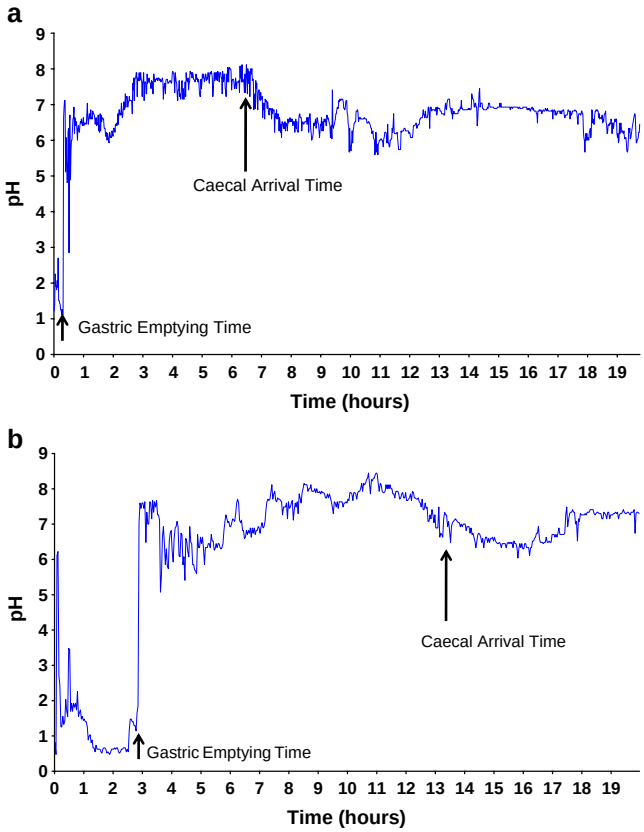

Fig. 2. **a** The gastrointestinal pH profile of subject 9 (fasted) on the first occasion; **b** the gastrointestinal pH profile of subject 9 (fasted) on the second occasion (1 week later). Volunteer 9 was not part of the main study.

become more pronounced distally, and the capsule underwent prolonged stagnation at the ileocaecal junction in one subject (volunteer 7). A way to overcome the difference in capsule and tablet transit would have been to tether the tablet and capsule together, but this would have adversely affected the transit data, and provided inaccurate reflections of "normal" tablet behaviour. However, for the purposes of this investigation, it is assumed that the pH experienced by the tablet approximates that measured by the pH capsule. For the tablet and pH capsule, statistical analyses showed no effect of feed state on the small intestinal transit times ($p>0.05$).

In Situ Tablet Disintegration

Several studies have correlated disintegration time of enteric dosage forms and drug release and have found a strong relationship between the two (25,26). Therefore in this study, Eudragit S coated tablet disintegration at the colon can be considered indicative of successful site-specific targeting. Tablet disintegration occurred in seven out of eight subjects in the fasted state, six of these disintegrating in the colon and one at the ileocaecal junction (Table IV). Tablet disintegration was experienced by five out of eight subjects in each of the pre-feed and fed and pre-feed states, with variable sites, mainly at the ileocaecal junction and the ascending colon (Tables V and VI). The site of disintegration confirms that Eudragit S coated pH responsive dosage forms demonstrate "ileo-colonic" targeting, rather than colonic targeting (9). The site or time of disintegration was not affected by the feeding regimen, although it was observed that more disintegration failures occurred in the fed and pre-feed states. *In vitro* studies by Ibekwe *et al.* (13) showed that drug release in buffer was slower from Eudragit S coated tablets after pre-exposure to acid for 2 h, compared to only 30 min. This is attributed to acid imbibing into the film, delaying the neutralising effect of the alkaline buffer media. This correlates with our results; the tablets administered with food, or before food, are retained in the stomach for longer and their exposure to acid is greater. This may make the coating dissolution more difficult and more tablets remain intact in the distal gut.

Failure to disintegrate of a colon-targeted coated system such as this is indicative of failure to release drug; in a study by Tuleu *et al.* (24) no disintegration of one colonic release capsule was observed and this was correlated with no detection of drug in the blood. The entire principle of successful colonic drug delivery with Eudragit S coated tablets is that they should, theoretically, disintegrate when their polymer coating dissolves after exposure to pH values greater than 7. This region of high pH occurs at the distal

Table III. Transit Times of Bravo® pH Capsule

	Time (min)							
	Gastric Emptying Time		Upper Small Intestinal Transit Time		Ileocaecal Junction Residence Time		Caecal Arrival Time	
Subject	Fasted	Pre-feed	Fasted	Pre-feed	Fasted	Pre-feed	Fasted	Pre-feed
1	69	80	222	280	84	170	375	530
2	40	26	85	99	98	355	223	480
3	83	301	207	76	23	235	313	612
4	75	185	285	145	132	122	492	452
5[a]	30	–[a]	250	–[a]	212	–[a]	492	–[a]
6	78	258	100	252	0	150	178	660
7	76	34	399	175	>365[b]	>631[b]	–	–
8	43	264	251	138	304	113	598	515
Mean (±SD)	62±21	160±127	225±100	170±82	122±107	190±91	381±154	541±80

[a] Subject 5 declined to swallow the Bravo® pH capsule
[b] Residence extended beyond the imaging time and these values have been excluded from the mean

Table IV. Transit and Disintegration Times of Eudragit S Coated Tablet (Fasted)

	Tablet Transit (Min)				Tablet Disintegration	
Subject	Gastric Emptying Time	Upper Small Intestinal Transit Time	Ileocaecal Junction Residence Time	Caecal Arrival Time	Disintegration Time (Min)	Location
1	68	99	81	–	248	ICJ
2	36	143	10	189	220	AC
3	79	107	88	274	462	AC
4	38	64	199	301	440	AC
5	15	155	43	213	Intact	AC[a]
6	164	97	83	344	444	AC
7	64	193	10	267	292	AC
8	43	251	76	370	515	AC
Mean (±SD)	63±46	139±61	74±60	280±65	374±117	

[a] Position of intact tablet at end of imaging
AC Ascending colon, *ICJ* ileocaecal junction

small bowel, which includes the terminal ileum and ileocaecal junction. Figure 3 shows the relationship between the time spent at the ileocaecal junction and the associated pH on whether the tablet disintegrates or remains intact. Out of the four tablets that remained intact in the fasted and pre-feed states, only three are represented in Fig. 3 as we do not have the pH measurements for volunteer 5 in the pre-feed state since he declined to swallow the pH capsule.

In subject 3 (pre-feed), the pH in the ileocaecal junction (distal small bowel) is 6.9, and the tablet spends only 36 min here, and fails to disintegrate. However, even when the *in situ* pH value experienced by the tablet was greater than 7, some tablets remained intact. For example, the tablet did not disintegrate in subject 5 in any treatment, suggesting an underlying reason may be inherent in this volunteer. The gastrointestinal profile of this subject (fasted) shows that pH was generally below 7.0 in the proximal intestine, rising above pH 7.0 distally in the ileocaecal junction. However, the transit of the tablet through this region is rapid (43 min), after which, in the colon, the environmental pH drops. This suggests that the length of exposure of a tablet to the correct pH may be a limiting factor. However, this was not seen in subject 4 (pre-feed); in this case the tablet spends a substantial amount of time in the small intestine exposed to a pH above 7 but does not disintegrate. The pH was highest in the ileocaecal junction, where the tablet spent only 15 minutes, and after entry of the tablet to the colon, the pH drops below the dissolution threshold of the polymer coating.

Examination of the effects of increasing pH and increasing ileocaecal junction residence time individually showed that although there was an increased likelihood that the tablet would break at the higher values, the relationships did not appear to be significant ($p>0.05$). Multiple regression analysis was used to assess whether the two variables combined had an effect on the tablet breakage but these were still found not to have a significant effect on the outcome. This is expected for an *in vivo* model which is influenced by more factors than we are able to control or assess, and suggests that the pH-responsive dosage forms are affected by much more than pH, and their behaviour is difficult to predict.

The evidence then suggests that we have to look further than pH, or even ileocaecal junction residence time, to understand the behaviour of these tablets. For example, the disintegration may be affected by upper small intestinal transit time (excluding stagnation at the ileocaecal junction). This is exemplified in Volunteer 8 (fasted). The pH is below

Table V. Transit and Disintegration Times of Eudragit S Coated Tablet (Pre-feed)

	Tablet Transit (Min)				Tablet Disintegration	
Subject	Gastric Emptying Time	Upper Small Intestinal Transit Time	Ileocaecal Junction Residence Time	Caecal Arrival Time	Disintegration Time (Min)	Location
1	20	72	132	–	224	ICJ
2	57	57	239	–	353	ICJ
3	245	180	36	461	Intact	AC[a]
4	210	196	15	471	Intact	AC[a]
5	16	119	10	145	Intact	AC[a]
6	240	133	26	399	454	AC
7	37	109	93	–	239	ICJ
8	54	71	140	–	265	ICJ
Mean (±SD)	100±109	106±43	95±81	354±181	307±96	

[a] Position of intact tablet at end of imaging
AC Ascending colon, *ICJ* ileocaecal junction

Table VI. Transit and Disintegration Times of Eudragit S Coated Tablet (Fed)

	Tablet Transit (Min)				Tablet Disintegration	
Subject	Gastric Emptying Time	Upper Small Intestinal Transit Time	Ileocaecal Junction Residence Time	Caecal Arrival Time	Disintegration Time (Min)	Location
1	137	62	55	–	254	ICJ
2	20	151	164	–	335	ICJ
3	273	47	70	–	390	ICJ
4	200	240	52	492	Intact	AC[a]
5	110	162	83	355	Intact	AC[a]
6	205	155	49	409	440	AC
7	119	84	97	300	Intact	AC[a]
8	219	258	–	–	477	TI
Mean (±SD)	160±79	144±78	81±40	389±82	379±88	

[a] Position of intact tablet at end of imaging
AC Ascending colon, *ICJ* ileocaecal junction, *TI* terminal ileum

7.0, but the tablets experienced a reasonably long transit period through the small intestine (251 min) eventually showing disintegration in the colon. Fluid volume plays an obvious role in the disintegration and dissolution of dosage forms and in the mean total water content of the small and large intestine has been reported to be just 206 ml (27), and 187 ml (28) respectively (at autopsy), but is highly variable between individuals and therefore likely to have implications for drug release. Of this total fluid, most is bound to digesta and only a proportion is free fluid available for interaction with dosage forms. This free fluid was identified by magnetic resonance imaging to exist as fluid pockets, the volume and distribution of which is not homogenous throughout the intestine. In the fasted state, the mean free fluid volume was 105 and 13 ml in the small intestine and large intestine respectively whereas in the fed state this volume decreased to 54 and 11 ml in the small and large intestine respectively (29). In the fasted state, the mean number of fluid pockets is four

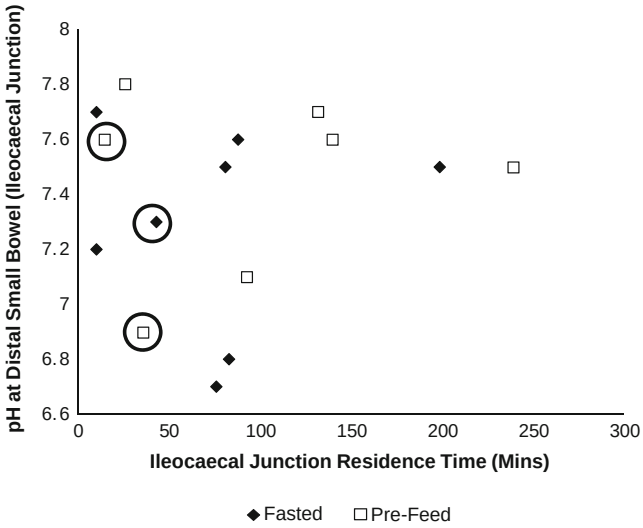

Fig. 3. The distal small bowel pH and ileocaecal junction residence time experienced by individual tablets ingested in the fasted state (fasted), or 30 min before food (pre-feed). The *circled points* indicate those tablets which remained intact.

in both the small intestine and colon, but the volume per pocket is 12 *versus* 2 ml respectively. There are also effects of fluid composition that are variable, and have been shown *in vitro* to affect dosage form behaviour; ionic strength, osmolality and buffer capacity of luminal content can affect dissolution of enteric coatings (13,30,31). Furthermore, these are known to change postprandially and are affected by the meal composition. For example, the resting buffer capacity in human proximal jejunal fluids increases from an average of 2.4 mmol l^{-1} ΔpH $unit^{-1}$ (fasted) to 14.6 mmol L^{-1} ΔpH $unit^{-1}$ (fed) (32). There is also inter-subject variability and postprandial changes in the quantities of phospholipid surfactants and bile salts (32) which can influence wetting and dissolution of polymer coated tablets such as this.

It proved difficult to draw firm conclusions about the effect of pH and transit on the performance of the pH-responsive dosage form since the sample size was small, the full data set could only be provided for three of the intact tablets, and the pH capsule was not administered in the fed state. It should further be noted that this study was conducted in healthy volunteers and the pH, transit and other aspects of GI physiology may differ in some disease states and there may be significant clinical implications of this and we already know that such tablets do not always disintegrate in patients (5,6). It does, however, become clear from our results and our consideration of other influential factors that the behaviour of pH-responsive dosage forms *in vivo* is much more complex than may have been previously anticipated and the efficacy and reproducibility of treatment with these systems cannot be assumed.

CONCLUSIONS

The study was designed to investigate the effect of the gastrointestinal pH and residence time on the disintegration behaviour of an Eudragit S coated tablet for colonic delivery. This was further correlated with feeding status. The *in situ* pH and intestinal transit demonstrated considerable variability and intra-subject variability was observed in one subject who ingested the pH measurement capsule on two different occasions. The propensity of the colon-specific Eudragit S coated tablet to remain intact (failure to disintegrate) during

the course of the study seemed to be affected by the feeding regimen. Only one out of eight tablets remained intact in the fasted state, but three out of eight tablets failed to break down under each of the fed and pre-feed regimens. This could have practical implications relative to dosage instructions, thus warranting further investigations. Although there appears to be a trend linking pH and transit times across the distal gastrointestinal tract with disintegration of pH responsive dosage forms, this was not been found to be significant. Disintegration of these systems *in vivo* appears to be complex, influenced by a multitude of physiological variables.

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