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Review

The transit of dosage forms through the colon

Clive G. Wilson*

Strathclyde Institute of Pharmacy & Biomedical Sciences, Glasgow G4 0NR, Scotland, UK

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ABSTRACT

Colonic transit is a subject of great relevance when considering *in vivo*/*in vitro* relationships for oral controlled release dosage forms. Our knowledge of colonic motility has first come from the clinic, where measurement of the whole gut transit of different excreted markers was used as a method of discriminating pathologies. X-ray contrast, although widely available, was used sparing due to the accumulating dosimetry associated with each exposure. Although such methods were used for swallowing studies, gamma scintigraphy allowed physicians to measure colon function with a more moderate radiation burden. The ability to label meal and dosage form separately and to measure dispersion with more certainty, prompted the use in pharmaceutical sciences; finally, the relationship between blood concentrations and transit of different sized dosage began to be understood. This mini-review considers the development of colon transit measurements and how different designs of clinical assessment assist in elucidating size and shape influence on colon transit in man.

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Abbreviations: 5-ASA, 5-aminosalicylic acid; C_{max}, measured maximum concentration; CCK, cholecystekinin; [^{51}Cr]-EDTA, chromium-51 labelled ethylenediamine tetraacetic acid; DTPA, diethylenetriaminepentaacetic acid; EDTA, ethylenediamine tetraacetic acid; ICJ, ileocaecal junction; In-111, indium-111; MRT, mean residence time (h); SITT, small intestinal transit time (h); SLIT, scintigraphic large intestinal transit (h); $T_{50\%}$, time for 50% movement of material from a region of the gut (h).

* Tel.: +44 141 552 4991; fax: +44 141 552 2562.
E-mail address: c.g.wilson@strath.ac.uk.

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1. Introduction

The interest in controlled release technology for oral drug delivery is largely driven by the prospect of increasing the efficacy of medicine with reduced side effects, maximizing patient compliance, patent extension, and perhaps novel methods of approaching the management of disease. The gut is designed for the absorption of food and specifically to avoid ingestion of poisons. It is a very efficient structure for digestion, and the delivery of the triturated food mass from the stomach into the intestine at an appropriate rate will maximize absorption. The colon apparently plays a relatively unimportant part compared to the small intestine; nevertheless the role in conserving water and electrolytes is well understood. In therapy, the additional surface for absorption of drugs prolongs the time of treatment for drugs that are transported through the tight colonic epithelium and for most formulations, colonic absorption represents the only real opportunity to increase the interval between doses. The transit of dosage forms through this region is therefore of great interest to the pharmaceutical scientist.

2. Colon: gross anatomy and physiology

The importance of the colon varies in mammals according to the nature of their diet. Thus true carnivores have a short colon with a small caecum whereas large ruminants have a high capacity caecum for fermentation, which may be separated from the ascending colon. The appendix in humans is vestigial and apparently unimportant in the human nutritional process. On opening the abdomen, the large colon is usually easily visible because the transverse loop has a very antral position in the abdominal cavity and may contain gas. Fig. 1 illustrates the main physiological features of the colon. The bacterial fermentation of ingested soluble carbohydrates yields carbon dioxide, and in some individuals if the redox potential is low enough, hydrogen and methane.

Compared to the small intestine it is shorter – 1.5 m rather than 5 m – and the lumen is wider, without the extra surface area provided by the folds of Kekring and the villi. The absorptive capacity for drugs is therefore markedly reduced but this can be balanced by the long periods of residence in the ascending colon. The major regions of the colon are the right or ascending colon; the transverse colon which is folded in front of the ascending and descending arms by the hepatic and splenic flexures; the descending colon which stores faeces and finally the rectum and anus. Overall the length of the human colon is approximately 150 cm, but only the last 30 cm is accessible from the anus, since the folding of the splenic flexure resists material entering the transverse colon if rectal delivery of large volume enemas is attempted. Targeting the first half of the colon is therefore difficult from a physiological perspective; however, the bacterial population provides a step change in luminal environment with a different set of metabolic enzymes to aid selective release. As an incentive, drug delivery to the colon has often been an attractive goal for peptide delivery as it is supposed that the lack of digestive enzymes would facilitate absorption. A drawback is the lack of fluid for dissolution and the environment is moist rather than full of fluid, with normal maximal water content of 30 ml recoverable postmeal from the caecum (Diakidou et al., 2009). When empty, the colon is collapsed with little motility but the transverse section may extend with gas following fermentation of the carbohydrate. The terminal segments may be occupied by stool and little drug absorption can occur from the distal regions under these conditions.

The wall of the ascending colon when scraped with a pH electrode gives an alkaline reading as high as pH 8, caused by secretion of bicarbonate by a sodium-dependent bicarbonate secretion which is non-chloride dependent (Sullivan and Smith, 1986). This secretion of the bicarbonate would be expected to render the colon alkaline, but this is balanced by the bacterial fermentation of carbohydrate to short chain fatty acids, particularly in the caecum and right colon. Studies with reliable pH electrodes implanted on the colon wall during colonoscopy in areas free of debris indicate that patients with a normal bowel have a more acidic right colon (pH 7.05 ± 0.32), followed by a more alkaline transverse colon (pH 7.42 ± 0.51), becoming more acid moving towards the rectum (pH

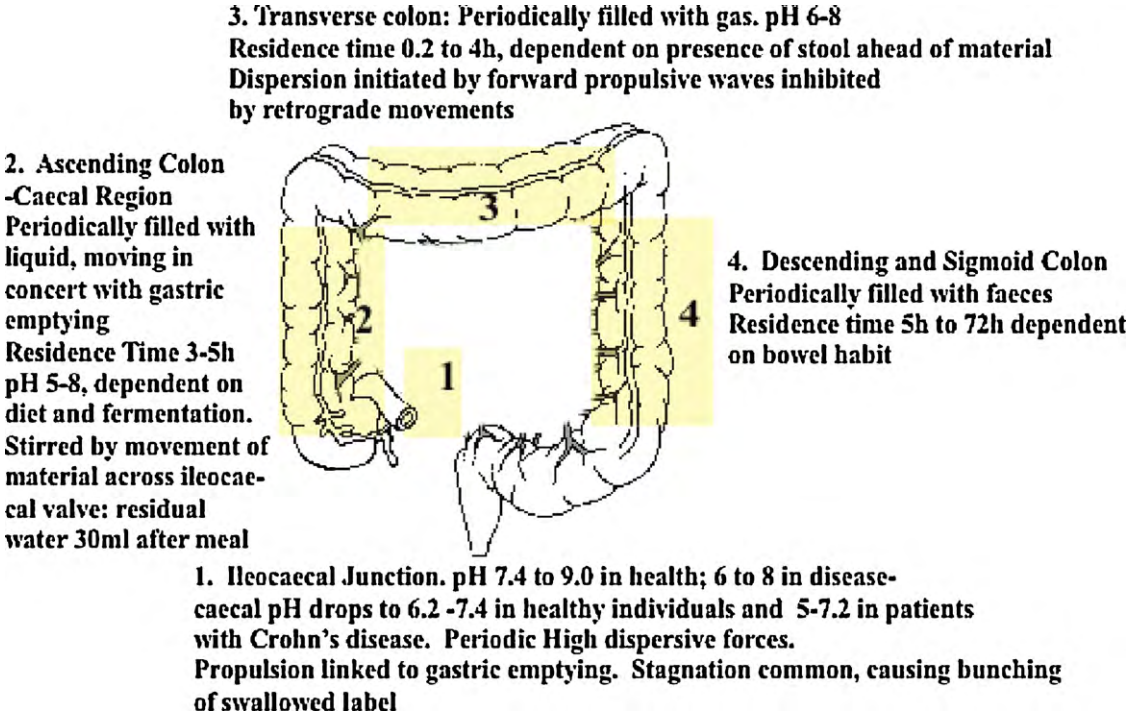

Fig. 1. Physiological features of the colon relevant to modified release dosage forms. Data from Press et al. (1998) and modified from a previous article (Wilson, 2008).

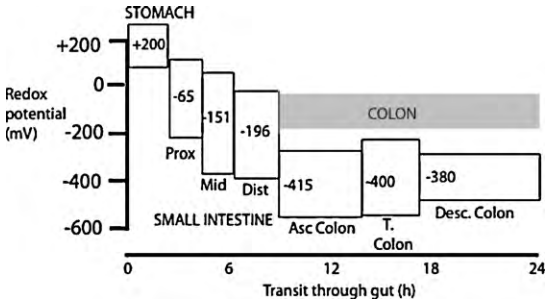

Fig. 2. Redox potentials in the gut. Modified from Stirrup et al. (1990). Boxes represent mean (mean value within box) ± 2 s.d.

7.15 ± 0.44). The lumen pH mirrors the changes of the wall, but remains consistently more acidic (McDougall et al., 1993). Press et al. (1998) report values illustrated in Fig. 1.

3. Redox potential

The principal end products of complex carbohydrate digestion by the colonic microflora are short chain fatty acids, carbon dioxide, hydrogen and methane. The colonization of the human gut by methanogenic bacteria varies between individuals and between gut regions, but all humans have a population of these commensals and when the number rises above 10^8 *Methanobrevibacter smithii* sp./g dry faecal weight, pulmonary methane can be detected (Miller and Wolin, 1986). The ability to shuttle electrons across suitable sources such as flavins and NADH through to organic sulphur allows reductive metabolism to occur in the anaerobic gut lumen. Azoreductase activity has been described in an aerobic *Bacillus* sp. isolated from soils which similarly uses oxidized flavin mononucleotide, which is NADH dependent and oxygen-insensitive (Ooi et al., 2007). Generally, the activity is associated with anaerobes such as *E. coli* (Rau and Stoltz, 2003). This principle would appear to favour colon targeting of drugs since in the colon, the bacterial population form a consistent community established by diet. Past reviews quote different values for colonic redox potential although the data appears to be drawn from the same sources in the literature (Stirrup et al., 1990; see Fig. 2). As will be discussed later, the redox environment of the colon is suspected to affect motility, since methane affects gut contractility.

4. Motility patterns in the colon

Motility of the intestinal smooth muscle must accomplish two objectives: mixing of the gut contents with enzymes and movement of nutrients towards the epithelial lining to accomplish assimilation and onward propulsion known as *peristalsis*. Equally, it must hold faecal matter in the descending colon until it can be voided and thus generate a counter movement, in a distal to proximal direction. The arrangement of the gut is an inner circular muscle as a tube, which squeezes, radially ensheathed by longitudinal muscle which propels content forward. The motility is controlled by autonomic nervous inputs from the splanchnic and vagal nerves, by plexuses which are interpolated between the two muscle layers, by local responses and finally from extrinsic loops between stomach and colon. The nature of the force and the time over which contractions occur shows marked differences for the colon compared to the proximal small intestine. The integration is complex and many pharmacological motifs will interplay with the diverse range of transmitters in different layers and sectors of the gut. Consolidation of luminal contents occurs from the middle of the ascending colon into a mass, which gradually becomes more homogenous and viscous.

In healthy subjects, the two types of motor activity can usually be recorded from the colon. These are occasional propulsive movements (mass movements), which are generally hard to record as they occur infrequently, and non-propulsive, segmental activity, which can be recorded as increases in luminal pressure. Most information concerning segmental colonic contractions has been gained from balloon catheter measurements of the rectum and distal colonic segments, as intubation further around the colon is difficult. Haggar et al. (2003) describe experiments in which pan colonic measurements were completed in 10 normal subjects and eight patients with idiopathic constipation. The subjects were required to swallow two silicone-coated catheters, each with five solid-state pressure transducers. The researchers paid particular attention to high amplitude propagating contractions, which were reduced in the constipated group (median 1.9 per 24 h) versus the normal controls (median 6 per 24 h). The intake of a meal clearly increased the motility in the caecum through to the splenic flexure for the first 30 min of the postprandial period in both normal and constipated patients.

The application of scintigraphic measurements describing whole gut transit was a significant advance in the investigation of large bowel physiology. Furthermore, this technique could be directly applied to examining the transit of dosage forms through the gut.

5. Measurements of gut transit

Gastric and duodenal ulceration were commonly encountered conditions in general practice and required surgical intervention if serious. Measurement of gastrointestinal transit, especially gastric emptying, was therefore a key task in medical physics and radiopharmaceutical investigation clinics. Colonic conditions were less frequently investigated, and modern developments in this diagnostic area occurred much later than those for stomach disorders. Investigation of large bowel function largely relied on complete gastrointestinal transit measurements. In the earliest established clinical methodology, patients were asked to swallow different coloured glass beads. The stools were then sieved to recover the markers (Alvarez and Freedlander, 1924). Hinton et al. (1969) described a method using radio-opaque markers of different diameters cut from barium-loaded polythene sheet or tubing which were swallowed with a drink and the stools collected to be X-rayed. This was compared to an earlier technique of stool collection following administration of [^{51}Cr]-sodium chromate and became the technique of choice until replaced by scintigraphy. Using products of different sizes, the transit rates and mixing patterns in the gut could be discriminated from abdominal radiographs. Hinton's method, although providing a robust off-line test, gave only a general idea of the transit of objects through the whole gut. The labelling of a test meal with [^{99m}Tc]-labelled sulphur colloid, which was already used for gastric empty measurements, was extended to allow gastroenterologists to make measurements of whole gut transit. It illustrated how conditions like diarrhoea involved earlier segments of the intestine (Read et al., 1986). Read's group noted that the caecum appeared to fill in a linear manner, with approximately 16% of the labelled meal residues entering the colon every hour. The shape of the filling curve mirrored that of gastric emptying curve, and from that a symmetrical bell shaped curve describing small intestinal exposure (SITT) was easily derived. The mean transit time through the small intestine was calculated to be 4 ± 1.4 h. Krevsky et al. (1986) from the Philips' group in the Mayo Clinic developed the concept of geometric centre analysis to calculate the position of the median portion of the meal, which was adopted as a method to describe the transit of formulations through the

gastrointestinal tract. This interaction was fruitful on both sides, and gastroenterologists started to adopt ideas from pharmaceutical research replacing labelled meals with labelled tablets and capsules which were more suited to routine radiopharmaceutical operations; for example, the scintigraphic large intestinal transit (SLIT) method in which the patient swallows 10 [^{111}In-labelled] size zero non-digestible capsules which are ingested after a 6-h fast (Stubbs et al., 1991). Scintigraphy remains a technique of choice for g.i. transit measurement since multiple components can be monitored simultaneously, for example meals and a formulation. Moreover, tablets of various sizes can be co-administered allowing discrimination of subtle differences in the regional transit of the formulations. The important factors were that subjects could remain upright and engage in normal activity, the dosimetry was low and allowed multiple measurements without increases in exposure. Non-invasive imaging allowed a multitude of factors to be investigated. More recently, other techniques including magnetic resonance imaging (Wilson et al., 1997; Schiller et al., 2005) and magnetic moment imaging (Weitschies et al., 1997) have added to our knowledge of the behaviour of dosage forms in the colon.

6. Colon arrival

The major variables in gastrointestinal transit of dosage forms are gastric emptying and colonic transit. Small intestinal transit times appear to be relatively fixed in man though can vary in and between individuals. Measurements indicate that there are only small perturbations caused by meal components such as fat. Early emptying of partially digested lipid, initiated by gastric lipase and perhaps backwash of proximal intestinal contents into the stomach, initiates the ileal brake. Following administration of a light meal, movement through the proximal gut is rapid and longer periods of stasis become evident as the formulation enters in the terminal ileum. Bunching of the formulation label is noticeable at the ileocaecal junction, immediately before entry into the caecum. Eating initiates propulsive activity and approximately 15 min after a meal, pulses of activity can be recorded in the sigmoid colon. Essentially, material is swept forward from the small intestine to clear a path for gastric effluent. In irritable bowel syndrome, the recordings are abnormal indicating distorted motility, which can lead to diarrhoea or constipation.

Throughout the day, colonic muscle is quiescent but large peristaltic waves – mass migration movements – can be generated by changes in posture especially in the morning. In clinical trial settings with morning dosing, small intestinal transit times in healthy adults are usually around 3–4 h and material swallowed in the morning is usually transferred into the colon by the intake of lunch or the thought of a mid-day meal. A note of caution: Cremonini et al. (2002) examining the reproducibility of these measurements, have commented that these data showed marked inter-individual variation. Notgi et al. (1994) also commented earlier that orocaecal transit times ranged from less than 2 h to more than 10 h.

7. Measurement of ileocaecal pressures

A common observation in scintigraphic studies is break-up of the dosage form as it moves from ileum to caecum. The formulation is forced through a functional sphincter which exerts a significant mechanical force on the dosage form and has been proposed as a method of achieving colon targeting (Takaya et al., 1995). The reliability of this method has not been thoroughly tested, although in studies employing scintigraphy and magnetic moment imaging, break-up of matrix units as they go though the ileocaecal junction is often observed.

8. Regional transit through the colon

The environment of the large bowel differs along its length and it is only in the right colon where conditions are sufficiently favourable to allow drug absorption. In the clinic, the first measurements of ascending colon transit times were performed by long tube studies, in which the subject was encouraged to swallow a dosing tube orally, down to the caecum. Under these conditions, very short proximal ascending loop transit times, 87.6 + 27.0 min were observed following the instillation of a liquid bolus into the caecum. Intubation and the CCK administered to accelerate transit were probably significant influences on this procedure (Barrow et al., 1981).

The transverse colon is frequently full of gas, and access to water is extremely limited. In the descending colon, the consolidation of faecal matter would inhibit dissolution and absorption of drug through the gut wall. The division of colonic transit into regional areas is therefore important in describing the transit of dosage forms through the colon and the possible impact on drug absorption. Gamma scintigraphy was immediately applied to the measurement of regional residence times, with a particular interest in the ascending and transverse loops of the colon.

Within the literature, three designs are usually encountered. The first is a clinical colon transit estimate using a single-phase marker such as Amberlite labelled with indium-111 or technetium-99m contained within a gelatin capsule or a meal. The second type of study is a comparative transit study using pellets and matrices simultaneously administered, but labelled with different radiopharmaceuticals. The third is a pharmacoscintigraphy trial in which non-absorbable marker such as technetium-99m or indium-111 ascertains the position of the formulation and blood levels are measured simultaneously.

9. Liquid markers

Many physicians used radiopharmaceuticals as supplied from the radiopharmacy, so early studies used solutions rather than labelled food components. Roberts describes a typical design for examining constipation in which patients are given the liquid on the afternoon prior to measurement, 18 h before measurements (Roberts et al., 1993). This observation is included here because we have few designs in pharmaceutics in which data is derived from dosing a liquid in the afternoon. The data from an analysis of 16 normal controls showed that 18 h, activity is distributed across the caecum and transverse colon.

10. Labelled meals

It was generally suspected that since liquids empty from the stomach at a different rate to solids that a more representative substrate – a labelled 536 kcal meal – would form an appropriate basis for a transit study. The technique pioneered at Sheffield utilized Tc-99m colloid incorporated into mashed potato (Read et al., 1986). The label was observed to appear in the caecum at 2.8 ± 1.5 h with 80% filling at 7.2 ± 1.9 h. In meal studies, two labels are often used for example technetium-99m added to meals as colloid in egg and the indium-111 labelled diethylenetriaminepentaacetic acid, [^{111}In]-DTPA, being given in the water. Graff et al. (2001) attempted to look for age and gender variation in gastrointestinal transit using this design and concluded that middle aged women had a significantly slower colonic transit, mean 61.5 h (range 38–80 h) than the younger women, 34.5 h (range 14–67 h).

11. Labelled monoliths

As scintigraphy replaced the Hinton method as a measure of gastrointestinal transit, there was a need to establish a normal range of transit times for diagnostic purposes. There were arguments about finer points of the methodologies and some differences in the selection of the marker: Stubbs for instance used capsules 21.6 mm × 1 mm tubing filled with In-111 and heat-sealed (Stubbs et al., 1991). The volunteers usually took multiple units to allow the spread of data to be more accurately described; in the Stubbs trial, 10 fasted subjects then each took 10 units following a 6 h fast and 3 days of standardized diets on two occasions and the regional transit data estimated from the combined individual measurements. These data are presented later. Price et al. (1993) also used Krevsky's analysis to measure the colon transit of 6 mm diameter tablets prepared from ethyl cellulose labelled with indium-111. Each subject took five units after a light breakfast with lunch at 4.5 h after dosing. As in the Stubbs' design, diet was controlled and transit measurements were multiple (three occasions). Price's study noted that the effect of lunchtime intake of calories was much more pronounced than that of dinner in terms of stimulating transit through the colon. This paper made a useful comment about the weakness of the geometric centre method in that it fails to provide useful data about large propulsive movements and tends to lose this detail in the data treatment. This is one reason why gastroenterologists started to subdivide Krevsky's analysis into smaller analytical parts, bisecting limbs of the colon. Bartholomeusz et al. (1999) took this to an extreme, constructing a mean colon line of 100 units from scintigraphic images from caecum to anus following administration [^{67}Ga]-citrate. It was noted that transport through was extremely variable – 2 to 6 h – with long periods of stasis at the hepatic flexure. Total mouth–anus transit times varied between 22 and 46 h. A comparison of these data with that derived from magnetic moment imaging shows why the latter technique is so useful, as it provides information concerning the three-dimensional movement through the gut. In this technique, an amount of ferromagnetic material varying from a few milligram (Weitschies et al., 2005) to just under gram (Wilson et al., 2007) is incorporated into the dosage form and magnetized. The resultant tiny magnetic field generated by unit, and the alterations in field strength produced by tumbling of the unit through the gut can be continuously recorded externally using a suitable detector array connected to a computer. When the tablet disintegrates, the signal is lost. If the quantity of magnetic material is small, sensitive shielded systems are used whereas larger amounts of ferromagnetic material permit usage in most locations. As an alternative, a small bar magnet is incorporated into the core of the tablet.

Basile et al. (1992) describe the application of diamagnetic methods to measure segmental transit of a steel sphere enclosed in a radio-opaque tube through the gut (resultant density 1.9 g cm^3) and calculated the mean mouth-to-caecum time of 13 ± 1.7 h in the supine position. The total colonic transit time was 43.5 ± 5 h in 12 healthy subjects. Approximately 35% of the residence time was spent in the right colon suggesting that more than 13 h contact could be achieved. This is, of course a much higher density than would be encountered in conventional formulations but the issue of density is worth considering further.

Using scintigraphy, the transit of capsules with densities of 0.8 and 1.1 g cm^3 was investigated in our laboratories (Parker et al., 1988). It was noted that densities in this range did not affect transit through the ascending colon. From these data, the $T_{50\%}$ was calculated as 7 h between entering the ascending colon and exiting to the transverse colon. In this study, subjects were fasted for 6 h prior to a meal of 4500 kJ. In investigations to compare the measurement of gastrointestinal motility using magnetic moment imaging and scintigraphy, oval tablet dosage forms (19 mm × 6 mm × 9 mm) containing iron oxide and labelled with [^{99m}Tc]-DTPA labelled lactose were administered to six healthy male subjects (Goodman et al., 2010). In two exposures, mean gastric emptying occurred at 95 ± 44 min and 89.2 ± 26 min, which is normal, but in two subjects in one arm of the study where the tablet stayed intact, longer small intestinal transit times (<5 h) were noted. Stathopoulos et al. (2005) made a similar observation, reporting a mean SITT of 315 ± 55 min (n = 9) for a cylindrical silicone coated magnet, dimensions ⌀ 6 mm × 7 mm length. He also reported observing slow rhythmical 'back and forth' movement whilst the magnet was in the caecum and ascending colon. Presumably, the onward propulsion of the magnet provided by muscular contractions was countered by the sinking back down to under gravity until the environment became drier.

Total gastrointestinal exposure will also be affected by prolonged residence in the stomach, with lower density formulations in a fed state acting as a gastro retentive system. Up until now, such a strategy has been confined to ensuring better absorption in the upper g.i. tract, often taking advantage of increased solubility of bases provided by acidic gastric conditions. Podczeck et al. (1999) compared the gastric emptying of ethylcellulose-coated tablets of different densities, ⌀ 12 mm and 6.6 mm. The first trial, conducted with 12 mm tablets (density 1.5 and 3.7 g cm^{-3}) administered fasted with 50 ml water suggested that density had an effect, but the differences between gastric emptying tablets were small and required frequent imaging to clearly discriminate behaviour. Two of the subjects in the cohort emptied the tablets at around the same time suggesting that other, physiological factors might be important. In the later study (Podczeck et al., 2007) the tablet size was reduced to ⌀ 6.6 mm with densities of 1.41 and 2.85 g cm^{-3} and the tablets co-administered to almost the same cohort of fasted volunteers as before. In this case a strong effect of density was observed with later emptying of the denser tablets. Overall, the gastric emptying times were longer than for the ⌀ 12 mm tablets, suggested that the dimensions of the pyloric cylinder are important. This potential for manipulation of gastric residence according to size and density will have consequences with regard to later colonic exposure and the effect of subsequent sequences of meals on ileal to colonic transfer of formulations.

In studies of the regional absorption of a paracellular probe [^{51}Cr]-EDTA and transcellular probe quinine, we utilized the timed-release system Pulsincap with different plug lengths to deliver the probes simultaneously to different regions of the colon (Hebden et al., 1999a). It was observed that compared to release in the small intestine, release in the ascending colon resulted in lower drug levels and still further reduction if the system released the probes in the transverse colon (6.26 ± 0.78% small intestine, 2.59 ± 0.52% transverse colon). No such gradient was observed for the paracellular marker with approximately 1% recovered in the urine. The lowest recovery was seen in the ascending colon, suggesting that this tissue might have particularly tight junctions.

12. Pellet transit through the colon

Transit of different size formulations through the colon has been a great interest since the early demonstrations of the differences between pellet and matrix movement. A tendency for transit rates to increase with increasing volume is noted (0.3 to 0.8 to 1.8 cm^3) although there appears to be a threshold size before this effect becomes dramatically apparent since, summarizing papers from our group cited in this paper, no difference between the ascending colon transit of 0.2 and 5 mm particles, or separately between ⌀ 0.2 mm, 5 mm and 8.4 mm particles was evident. If subjects are dosed with labelled pellets every day until a quasi-steady state is achieved, the calculated ascending colon residence time becomes

longer. In healthy subjects, an asymmetric distribution of pellets occurs between the proximal and distal limbs.

Other, earlier studies made observations as far as ileal to caecal transfer and then closed the measurements, for example Clarke et al. (1993) followed the earlier work of Devereux et al. (1990), who reported that high density pellets (⌀ 1 mm, 2.8 g cm^{-3}) were slower to empty from the stomach than those of a density of 1.5 g cm^{-3}. Clarke's group compared two densities, 1.5 and 2.6 g cm^{-3}, and two sizes ⌀ 0.5 and 4.75 mm in a scintigraphic study in eight fasted subjects. They noted that onset of gastric emptying was not affected by size and density but time of caecal arrival was affected by density for both diameters of pellets, with an increased small intestinal transit time due to density. In some subjects the difference was marked, especially for the large tablets, whereas in others it was a modest 20 min or so.

13. Tablets and pellets co-administered

The early studies carried out in our laboratories attempted to compare the transit of technetium-99m labelled pellet in a gelatin capsule with a monolith labelled with indium-111. Initially, we were not interested in the subsequent transit of the formulation through the colon and finished data collection once all of the material had entered the caecum; however, the technique lends itself to investigation of colon transit extremely well (Hardy et al., 1985). The transit of a gelatin capsule containing 200 mg Amberlite IR-120 (H) pellets was compared to a co-administered radiotelemetry device 25 mm long × 9 mm diameter. In fasted volunteers, it was observed that when administered with 200 ml water at 0900 h, the capsule broke up in the stomach releasing the pellets as a series of boluses. Both the monolith and the labelled resin arrived at the ileocaecal junction at approximately the same time. In this first study, the small number of subjects and the complicated lunchtime regime [two subjects fasted, two subjects fed at 3 h, two subjects fed at 5 h] contributed far too much variability although there were a couple of important general observations. Firstly, formulations administered after overnight fasting tend to arrive at the colon around 1 pm; approximately 5 h after dosing which was also confirmed in later studies. Second, once in the colon the monolith moved ahead of the labelled pellet mass with an average residence time of 4.7 h in the ascending colon (range 0.7–7.5 h). The monolith reached the transverse colon before 86% of the pellets. Transit was longer in the fed subjects versus the subjects who remained fasted. At 24-h, the monolith had been excreted or was at the rectosigmoid junction with pellets distributed between the ascending and the descending colon with little material in the transverse colon. At the time, it was not noticed that the mid-day meal had a much bigger effect on colon transit than the evening meal and it was lamely concluded that eating was without effect on transit, which in retrospect is misleading. In a recent study, it was noted that ingestion of food whilst a tablet was in the ascending colon tended to move the unit into the ascending colon, or if the tablet was in the transverse colon, it moved it further along (Hodges et al., 2009). This provided a good illustration of the propulsive ileo-colic reflex, sometimes mistakenly termed the gastrocolic reflex. Misiewicz (1975), in a classical paper on colonic motility, referred to his earlier study (Holdstock and Misiewicz, 1970) and pointed out that this phenomenon occurs in patients who had undergone a total gastrectomy and therefore gastrin is unlikely to be involved. It is now appreciated that both the composition of intra-lumenal intestine contents and gastric distension-triggered signals may potentiate each other in producing abnormalities of gastrointestinal transit, including bloating early satiety and nausea (AMS Task Force, 2005). Returning to the scintigraphy studies, it was found that where the tablet was in the small intestine, food moved the unit on to the ileocaecal junction and stasis was observed. This observations supports the findings of Adkin et al. (1993)who observed that tablet stasis at the ICJ was more pronounced in volunteers where the tablet had yet to reach the end of the small intestine ahead of consumption of lunch. In later experiments (Hebden et al., 2000), we appreciated that the transverse colon serves as a conduit and material and the daily distribution results in one-third in the ascending colon and two-thirds in the descending colon.

In the clinic, the concept of using an enteric-coated capsule containing pellets was very attractive: the patient could be dosed the night before and return to the clinic the next morning. Simple procedures for coating with acrylic copolymers such as Eudragit S-100 were employed. Proano et al. (1990) describe a comparison of ascending colon transit times using this new method with that for radio-opaque markers. Transit through the ascending colon was 9.9 ± 3.8 h for the opaque markers and 11.9 ± 2.0 h for the [^{111}In]-labelled pellets. For whole colon transit the differences are amplified: 26.2 ± 8.3 h for the opaque markers and 35.7 ± 6.0 h for the [^{111}In]-labelled pellets. This difference reflects the differential transit of tablets and pellets: effectively a sieving mechanism. Proano et al. (1990) comment that their observations are exactly as we observed earlier (Hebden et al., 2000). This suggests that the propulsive movements are less effective for particulates, which perhaps stick to the colon wall rather than remain in the luminal flow.

Abrahamsson et al. (1996) conducted a study in fed individuals, comparing the gastrointestinal transit of a round 9 mm diameter placebo labelled with 99m with a metoprolol CR tablet labelled with [^{51}Cr]-pellets. The doses were given after feeding a breakfast and there was a regular meal sequence throughout the day at 4, 6, 10, 13 h, etc.

The effect of the meals on gastric emptying was pronounced: pellets arrived much earlier at the colon than the tablets (average pellets = 6.7 h, tablets 11 h). As in the studies reported by Cremonini et al. (2002), it was observed that there were individuals with faster transit of both pellets and tablets than the rest of the cohort without displaying a change in bowel-emptying frequency. Total colon transit times were reported rather than any regional analysis. These were 28 ± 14.5 h for pellets and 15.2 ± 8.7 h for tablets. It was noted that the effect of mass migrating movements was greater on tablets than on pellets, with sudden movements of the tablet after long periods of stasis.

14. Effects of water content of the colon

Changing the water content of the colon by pre-administering 20 g of lactulose for 3 days prior to administration of a capsule containing tablets and beads markedly increases the dispersion and dissolution in the transverse colon (Hebden et al., 1999b). This manoeuvre is used to simulate a diarrhoeal state in the colon where a patient's stools will contain more water. Normally, release of the drug payload from an enclosed system – in this case a Pulsincap – would fail to show dispersion of the contents in the transverse colonic region; however, lactulose pretreatment caused both an increase in transit through the ascending colon (from 4.5 ± 1.4 h to 3.7 ± 0.8 h) and greater absorption of the released probe, quinine (from 3.02 ± 0.63% to 4.66 ± 0.78%). In contrast to lactulose, pretreatment with codeine 30 mg q.d.s. for 3 days resulted in slowed transit through the transverse colon (8.9 ± 1.8 h), and slightly diminished the absorption of the quinine probe (2.6 ± 0.77%).

In another design to measure the effects of laxatives on the colon, three capsules were administered each containing 100 mg resin (mean diameter 0.2 mm) labelled with indium-111 together with 3 mm × 5 mm tablets labelled with technetium 99m. The capsules were then coated with Eudragit RS® and administered groups of healthy volunteers. In the control group, the mean transit time

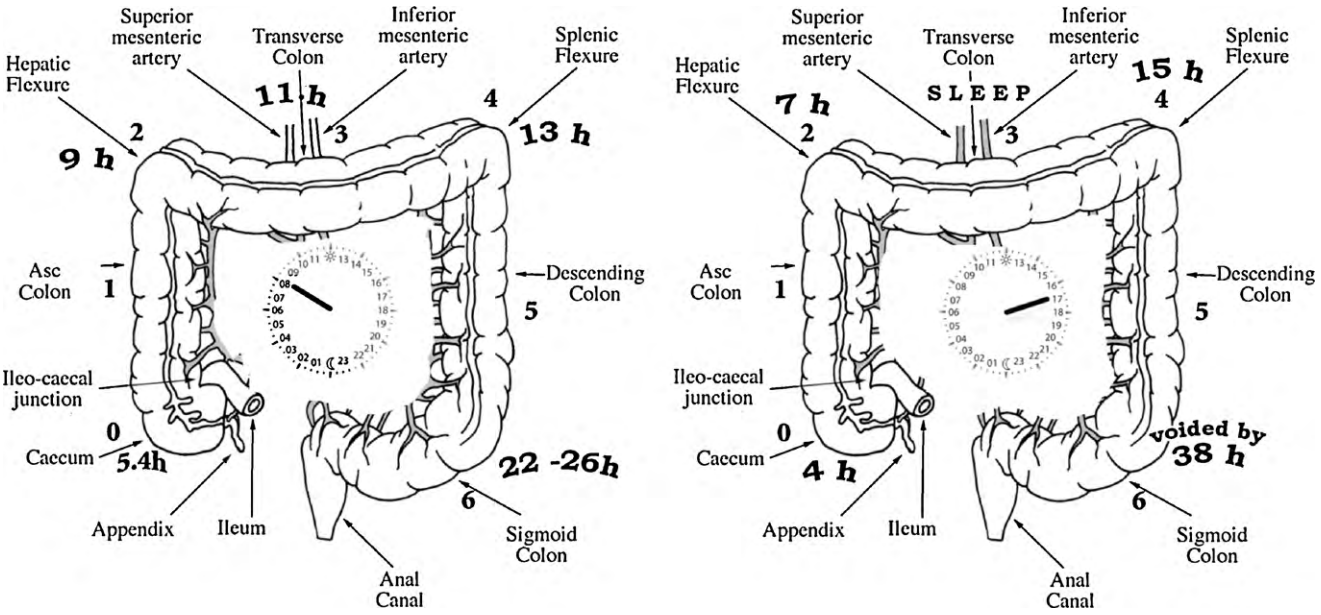

Fig. 3. Comparison of morning and afternoon dosing on transit of a [^{111}In]-labelled unit through the colon. Numbers represent the datum points used for the Krevsky analysis and timing, the mean time that the units appeared in succeeding segments of the colon.

for the particles through the ascending colon was similar for both the small tablets and the pellets (MRT for tablets = 13.7 ± 5.5 h; MRT for pellets 12.9 ± 3.7 h). Although the tablets had left the ascending colon by 24 h, 23 ± 13% of the pellets were still in the ascending limb (Watts et al., 1992).

Finally, we attempted to simulate an acute diarrhoeal episode by consumption of lactulose and to reverse the symptoms with codeine (Barrow et al., 1993). Co-administration of [^{111}In]-labelled 0.2 mm Amberlite resin with [^{99m}Tc]-labelled Amberlite® resin 5 mm tablets within an enteric coated tablet that broke up at the ileocaecal junction, showed that mean $T_{50\%}$ ascending colon transit time of the 5 mm tablets was extended by codeine treatment (30 mg q.d.s.) from 4.7 ± 3.4 h to 10.4 ± 7.7 h whereas the effect on the smaller pellets was much more modest: 5.3 ± 2.5 h extended to 7.4 ± 2.5 h.

15. Morning versus evening dosing

Although morning dosing after an overnight fast is a common regimen in dosing, it is probably not optimal in terms of maximizing contact with the ascending colon. When waking and moving around in the morning, mass movements can move formulations onwards but thereafter units administered in the evening have a slow colonic transit during the morning, since the intake of a small breakfast does not initiate a large gastrocolic reflex. To study night-time quiescence of the gut, a size 00 technetium-99m labelled monolith composed of labelled bone cement was administered simultaneously with resin pellets (0.1–0.3 mm) labelled with indium-111 and placed in a gelatin capsule which was subsequently dip-coated with Eudragit S-100® (Hebden et al., 1999c). Subjects were dosed either at 0800 or 1700 h and distribution of the marker compared at 8 and 15 h. It was observed that colonic transit of the pellets was marked reduced following evening dosing and that transit in the evening was faster than that during the morning. Immediately on rising, the mass of the resin had hardly moved from the ascending colon. Thus the colon 'goes to sleep' on retiring and propulsive colonic motility then increases, especially during the first 30 min even whilst still fasted. When radioisotope resin is administered each morning until steady-state [4 days], the transverse colon is generally seen to be relatively empty during the day. The important movements are a right side to left side propagation, residence in the site being generally influenced by the pattern of defaecation.

Total transit time was compared for OROS devices dosed at 0800 or 2200 h using faecal excretion of the unit by Sathyan et al. (2000). Whereas a unimodal distribution of excretion with maxima at 24–32 h after dosing was seen with morning administration, evening dosing resulted in a bimodal distribution with peaks around 12 and 34 h. This suggests that bowel habit is a key component in comparisons of whole gut transit. Coupe et al. (1992a) reported median transit times using scintigraphy of 29 h in one study and 35 h in another (Coupe et al., 1992b) following night-time dosing versus median transit times following morning dosing of 24 and 26 h.

Comparison of night-time versus morning dosing shows that there are large differences due to bowel habit and daily activities. Stubbs et al. (1991) dosed volunteers at 6 pm after a 12 h fast, allowed the subjects to sleep and then made measurements throughout the next day. This group reported very long transit times for evening dosing: our data suggests that the differences are marked but in our case the dosing was at 5 and not 6 pm. Typical data for a capsule from our own studies are illustrated in Fig. 3.

16. What is normal transit?

The definition of values for "normal" transit has occupied gastroenterologists for more than 30 years. Wagener et al. (2004) pose the dangerous question in an attempt to define abnormal values in constipation. In truth, the subtleties caused by feeding and activity patterns seem to have escaped many and there is an awkward statistical issue, which confounds the definition of a single value. As can be seen from the diagram, the distribution of transit times is clearly bimodal and, in my view, the central mean and standard deviation is utterly meaningless. Nevertheless, such figures are often quoted! (Fig. 4).

17. Population subsets and gastrointestinal transit

For poorly soluble drugs, the contact with the small intestinal epithelium is a critical determinant of drug absorption. Within

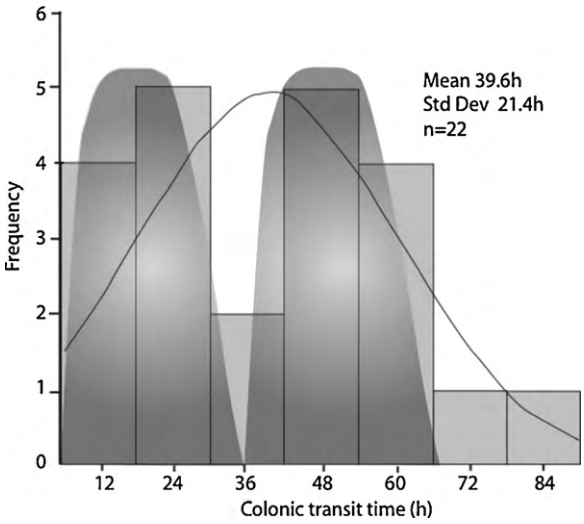

Fig. 4. The distribution of colonic transit times in children ($n = 22$) from the data of Wagener et al. (2004). A suggestion for an alternative statistical treatment is shown.

populations, there are usually a percentage of a sample who have a faster than normal transit, usually about 20–25% of a recruited cohort. Unfortunately has never been fully documented and is simply an observation of more than 20 years of gamma scintigraphy studies. Delayed gastric emptying and faster colonic transit had previously been noted for smokers (Scott et al., 1993; Rausch et al., 1998), where nicotine may be expected to have an effect on motility or young athletes, where the tight coupling of transit and extraction of nutrients might be advantageous to allow increased throughput of food. Our research group published a review of pathological influences on colonic motility in the early '90's (Barrow et al., 1981).

In the clinical development of gefitinib formulations, a subset of around 18% of the healthy subjects recruited into single dose studies showed a different pharmacokinetic profile for the drug than the majority of the dosed cohort. The profile was characterized by a faster elimination and a lower C_{max} resulting in lower systemic exposure and was consistent over long time periods. To examine whether gastrointestinal transit was an important variable, subjects were selected from the fast excreter group ($n = 5$) balanced against the normal ($n = 7$) volunteers (Wilson et al., 2009). The volunteers were dosed with a 250 mg gefitinib tablet labelled with [^{111}In]-DTPA. Blood samples were taken and it was found that the rapid excreters had faster gastric emptying and faster colon filling approximately halving the small intestinal exposure.

18. Influences on colon motility

18.1. Products of fermentation

18.1.1. Methane

It has been established by several workers that if the colon can support sufficient methanogenic bacteria and the diet is appropriate, the redox potential is sometimes low enough to generate methane. Pimentel et al. (2006) showed that methane has an effect on colonic contractility in those patients with irritable bowel who were methane rather than hydrogen producers. Methane producers were noted to have a higher fasting motility index than those who produce hydrogen. In fistulated dogs, methane introduced into the gut increased gastrointestinal transit. The group drew parallels with the discovery that nitric oxide which is able to facilitate many neuronal mechanisms in the body.

18.2. Short chain fatty acids

Food influences gastrointestinal transit by obvious mechanisms but the extent to which diet alters transit remains a topic of interest in the literature. Short chain fatty acids generated by fermentation of complex carbohydrates, notably butyrate and propionate, appear to have key roles in maintaining the integrity of the colonic mucosa and affect motility. This effect seems to be mediated through endocrine pathways, probably involving polypeptide YY secretion (Cuche et al., 2000). Cherbut (2003) drew attention to the dose dependency of the effects of short chain fatty acids on motility, supporting the argument that dietary influences are very important factors in colonic exposure. The role of gut microflora on gastrointestinal physiology is extensively reviewed by Rambaud et al. (2006).

19. Pathology

Pathological effects on colon transit are well documented, as the generation of normal clinical ranges for physiological factors has to be established as a function of age and gender. Colon transit is influenced by central, local and hormonal influences as the integration of gut motility occurs through intrinsic and extrinsic pathways. Thus spinal cord injury delays either proximal to mid, or distal to mid transit according to the site of the lesion (Media et al., 2009).

20. Conclusions

The influence of disease on the colonic transit of drug formulations remains an important area of study and is particularly relevant to the efficacy of topically acting drugs such as 5-ASA during acute flare of the disease. Increased fluid content and increased motility would be expected to produce opposite effects on drug absorption. Clarification of the impact of these two variables would assist in the design of treatment regimens.

Transit through the colon is largely influenced by the pattern of feeding and the time of day when dosing occurs relative to meal times. Other important influences are posture, size of dosage form and for part of the population, an inherent faster rate of transit of unknown aetiology.

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