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Review

Oral modified-release formulations in motion: The relationship between gastrointestinal transit and drug absorption

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ABSTRACT

Oral modified-release dosage forms can be designed with the aim of achieving specific pharmacokinetic profiles, delivering to specific gut localities or reducing the number of drug administrations. Multiple-unit systems, such as pellets, beads or granules, often claim superiority to single-unit modified-release formulations in terms of predictability and reproducibility of behaviour in the gastrointestinal tract. This is an oversimplification and in this review we discuss the effect of the highly variable gastrointestinal transit on the bioperformance of multiple-unit dosage forms, relative to their single-unit counterparts. We examine the sometimes contradictory literature in this area and highlight specific case studies which demonstrate the effect of intestinal transit on dosage form performance and drug absorption.

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1. Introduction

A modified-release oral dosage form is normally exposed to a multitude of conditions on its journey through the gastrointestinal

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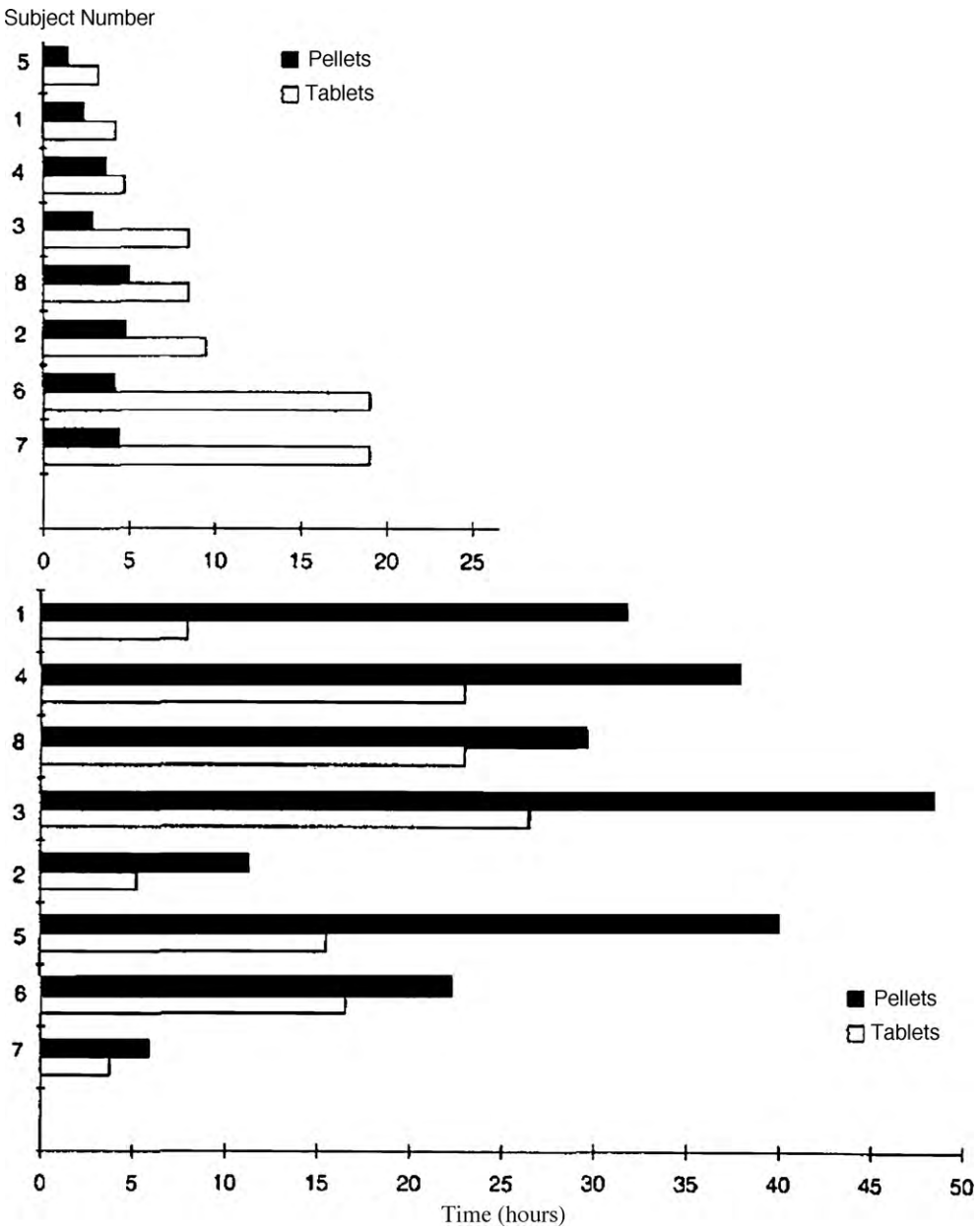

Fig. 1. Gastric emptying (top) and colonic transit (bottom) of single-unit (9 mm tablets) and multiple-unit (0.5 mm pellets) systems in the presence of food (Abrahamsson et al., 1996).

tract in comparison to a standard immediate release formulation. It then follows that its *in vivo* behaviour can be complex and variable given the plethora of interacting mechanisms going on in the gut (McConnell et al., 2008a). Gut physiology and the mechanisms of digestion and absorption have been extensively studied, and although we understand a great deal about what may be going on in the gastrointestinal tract, there are still gaps in our knowledge. Transit in particular has been studied for many years, but its complexity, especially in relation to modified-release dosage forms, is not fully understood.

Modified-release dosage forms can be formulated either as single-unit or as multiple-units, the latter where the formulation consists of many, often small-sized, units (pellets, beads or granules) which are either filled in a capsule, a sachet or are compressed as tablets which disintegrate to release the individual units (Follonier and Doelker, 1992). The purpose of this review is to compare and discuss the *in vivo* performance of single and multiple-unit modified dosage forms, highlighting the role of gastrointestinal transit on drug absorption.

2. Gastrointestinal transit of dosage forms

Gastrointestinal transit of solid dosage forms relies on gut motility and flow, which depends and varies on the type and timings of meal ingestion and the nature of the formulation. This information on dosage form transit has been gleaned from the use of imaging modalities, including traditional X-ray methods using radiopaque markers (Hinton et al., 1969) and more sophisticated methods such as gamma scintigraphy (Wilding et al., 2001), magnetic marker monitoring (Weitschies et al., 2010), magnetic resonance imaging (Richardson et al., 2005), and AC biosusceptometry (Corá et al., 2010). Also noteworthy is that dosage form transit through the gut is not continuous and even retro-propulsion can occur (Weitschies et al., 2005; Goodman et al., 2010). Moreover, gastrointestinal fluid

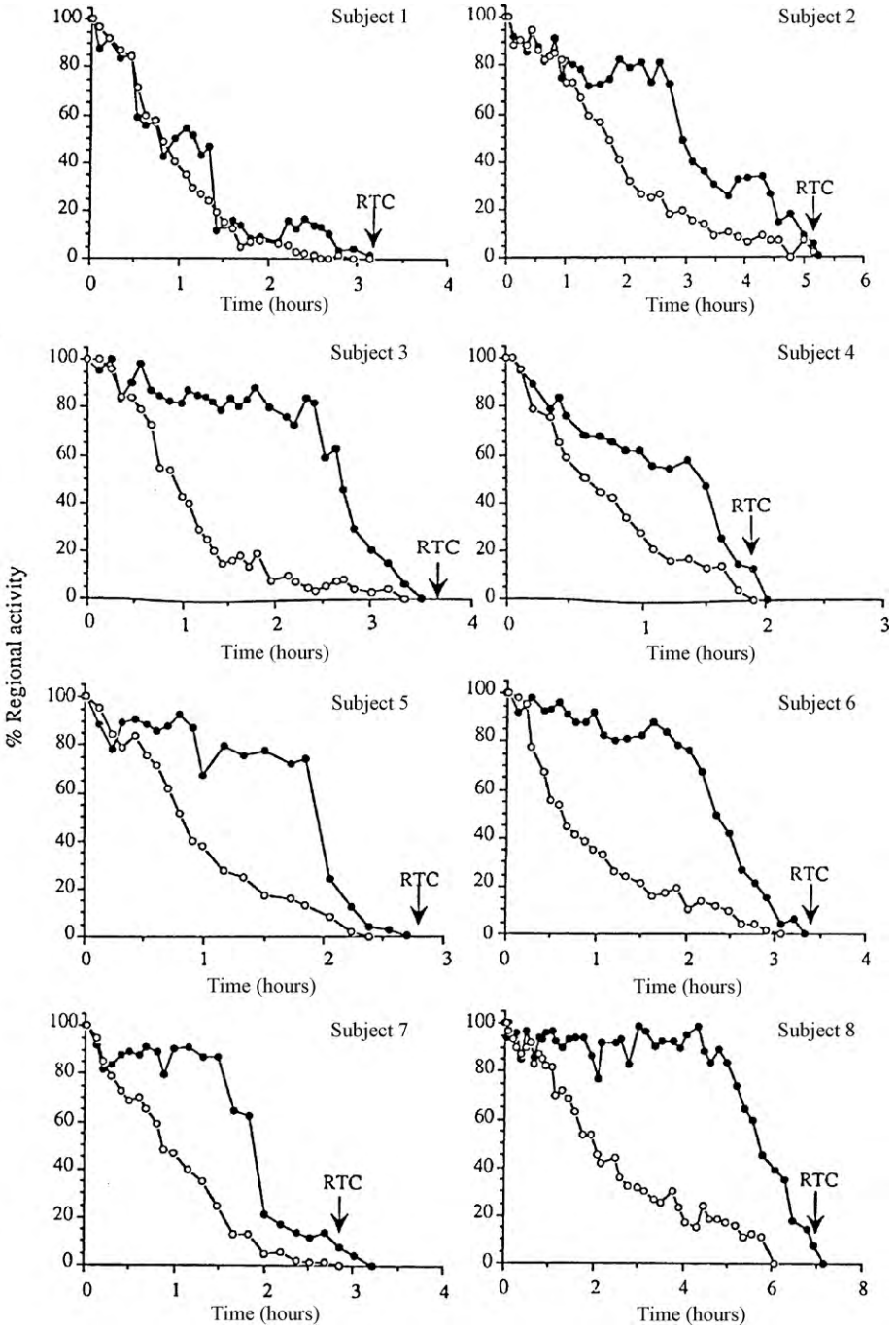

Fig. 2. Gastric emptying profiles of pellets (solid circles), food (open circles) and a radiotelemetric capsule (RTC) for all eight subjects (Coupe et al., 1993).

is not continuously available but is found in clusters; single-units may experience periods without contact with fluid during transit as this is an all or nothing event, contrary to multiple-units that, due to their spreading, are more likely to be at least partially exposed to the available fluid (Schiller et al., 2005). Gastrointestinal transit for a modified-release dosage form could be thought of as a starting and stopping process, sometimes moving quickly, sometimes slowly, sometimes passing through fluid of varying composition, and being subject to peristaltic pressures and forces.

Gastric retention and gastric emptying are the first challenges a dosage form will face. It is known that in the fasted state gastric motility is under the control of the migrating myoelectric complex (MMC) whereas in the presence of food, the MMC is disrupted and is replaced by fed state contractions. This is something of an over-simplification, and it is worth highlighting that some MMC cycles bypass the stomach completely and originate in the small intestine, which may contribute to a longer gastric retention of modified dosage forms, particularly, single-units in the fasted state (Kellow et al., 1986) which usually rely on the strong sweeping contractions of the "housekeeper wave" to undergo gastric emptying.

In the fed state, the distal stomach has a peristaltic activity which mixes and mills solids, and ensures a controlled evacuation of chyme into the duodenum. The duodenum also plays a role in gastric emptying in this fed state, responding to the osmotic pressure and energy content of digestion products of food; the greater the caloric content of a meal, the lower is the volume transferred to the duodenum (Hunt and Stubbs, 1975; Hunt et al., 1978). The stomach exhibits a maximum gastric emptying rate

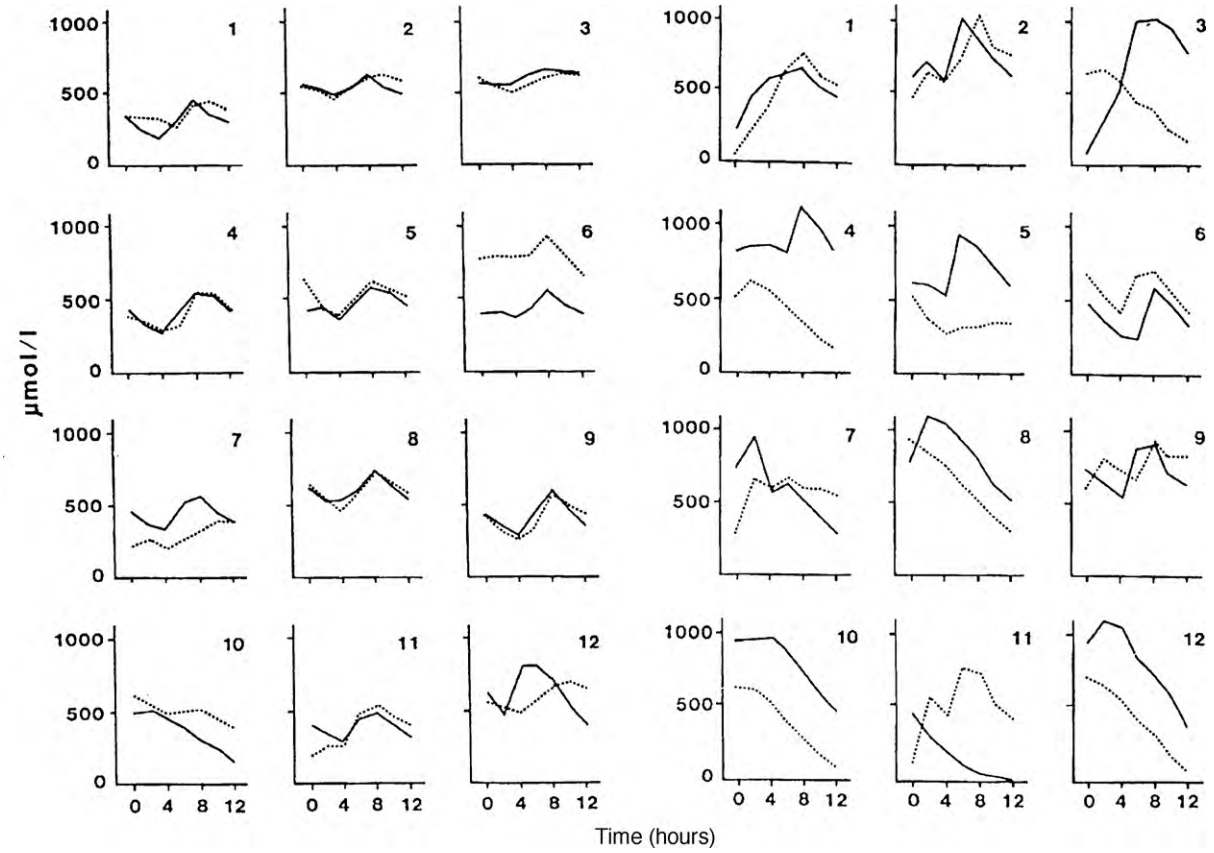

Fig. 3. Individual plasma concentrations of salicylate over two consecutive days, day 1 (dotted line) and day 2 (bold line) after administration of (left) enteric-coated granules and (right) enteric-coated tablets (Edgar et al., 1984).

of 200 kcal/h (Hunt, 1983). It is evident that gastric emptying is controlled by many mechanisms, and is further influenced by the range and quantities of liquids and solids that we choose to ingest. This led to the apt statement by Olsson and Holmgren (2001) that "almost everything seems to affect gastric emptying", an issue that becomes problematic when controlled and reproducible behaviour of modified -release dosage forms is necessitated.

It would seem a logical assumption that the larger the dosage form, the longer the gastric retention that would occur, as the stomach attempts to mill the solid down to a manageable size. However, this is not always the case and the evidence confirms that the process is much more complex than this. Gastric emptying of pellet formulations (size 0.5–1.7 mm) (Clarke et al., 1995; Basit et al., 2004) was found to be similar to larger single-unit dosage forms (15.9 mm × 7.1 mm) (Wilding et al., 1992) from the empty stomach. Similar results were shown with a light breakfast in a study by Sugito et al. (1990). This contrasted to studies in which it was shown that gastric emptying of multiple-units (pellets), administered simultaneously with a tablet to healthy volunteers after a light breakfast, was faster compared to the single-unit (Davis et al., 1984b). This trend was also seen when pellets (compressed as tablets) were administered after a heavier breakfast (2800 kJ). The non-disintegrating tablets (9.0 mm) were cleared from the stomach, approximately, 3 h later than 0.7 mm pellets (Fig. 1) (Abrahamsson et al., 1996). In fact, gastric emptying of single- (Waterman, 2007) and multiple-units (Davis et al., 1984a) has been shown to be progressively delayed as caloric content of the food ingested increased. The delay was more pronounced for tablets, which failed to empty in volunteers who consumed a high caloric meal (3600 kJ) for up to 10 h post-dosing (Davis et al., 1984a). Obviously, in this case, the tablets remain in the stomach long after the food has been expected to have emptied, and in a study by Coupe et al. (1993) the authors suggest that pellets are also cleared from the stomach after food. As a caveat it should be noted that in two of the eight subjects, the meal and pellet formulation actually emptied from the stomach at similar rates which clouds the issue somewhat (Fig. 2).

This faster clearance of multiple-unit dosage forms in the fed regimen was not shown with 1 mm pellets, and no significant difference was noticed in their gastric emptying (105 ± 45 min) compared to 11 mm single-unit (90 ± 35 min) dosage forms (Coupe et al., 1991). Similar observations were found for gastric emptying of 2 and 10 mm radiopaque markers (Smith and Feldman, 1986); and 5, 6, and 7 mm tablets (Khosla et al., 1989). This lack of size effect on gastric emptying was also observed for multiple-units of different sizes. Surprisingly, Podczeck et al. (2007) reported a shorter gastric emptying time of a 12.0 mm tablet than a tablet of 6.6 mm, irrespective of density, further complicating the effect of size on gastric clearance. Interestingly, the time of day at which a dosage form is taken can affect its transit. Night time administration can extend the gastric residence time of single-units (Coupe et al., 1992a) but no such study has been reported for multiple-unit dosage forms.

We have discussed the differences/similarities between the gastric emptying of quite different dosage forms (i.e. very small vs. relatively larger), but we can also consider the gastric emptying of dosage forms which are closer in size, e.g., pellets of differing dimensions. In fact, no significant difference on gastric emptying was found between smaller pellets (0.5 mm) and larger pellets (5.0 mm) in healthy volunteers in the fasted state suggesting that the size of dosage form is not determinant of the stomach clearance

in the absence of food (Clarke et al., 1993). Also, no differences were observed when pellets were dosed either as a tablet (compressed granules) or a sachet (Wilding et al., 2000). However, as noted above with pellet and tablets, significant differences were noticed in the presence of food and small pellets (0.7 mm) were emptied half an hour before larger units (3.6 mm) (Choe et al., 2001).

The aforementioned scenarios deal primarily with the (a) fasted and (b) fed states (i.e. (a) where the stomach is undergoing the MMC after a 12 h fast and (b) where the dosage form is taken with, or within 30 min of, food). There are other scenarios to consider, for example, administration of a multiple-unit formulation 30 min before food (pre-feed regimen) resulted in faster gastric emptying compared to when no food was administered. This suggests that food intake lead to an increase in gastric motility and consequently to a faster gastric emptying (Digenis et al., 1990).

Small intestinal transit time is almost invariably quoted at 3–4 h and reported to be similar for tablets, pellets and liquids (Davis et al., 1986). Perhaps less than half of this time is spent in actual transit, a dosage form spending considerable time at rest in the small intestine (Weitschies et al., 2010). However, considerable inter- and intra-subject variability of small intestinal transit times for multiple- and single-unit systems has been reported, with values ranging from 0.5 to 9.5 h (Davis et al., 1986; Sugito et al., 1990; Coupe et al., 1991). Small intestinal transit of pellets has been recorded from 1.5 to 5.4 h in the same person on eight separate occasions highlighting a large degree of intra-subject variability, where only on two occasions transit time fell within the often-stated 3–4 h average (McConnell et al., 2008a). It has also been observed that pellets do not distribute widely in the small intestine and tend to move as a bolus (Davis et al., 1984b), contrasting to previous assumptions.

In traditional fasted/fed regimens no significant effect of food was observed on small intestinal transit of dosage forms (Davis et al., 1986); the data is often so variable and overlapping that fed/fasted trends have never been elucidated. However, it was observed that administration of multiple-unit enteric-coated dosage forms before food (pre-feed) resulted in a faster small intestinal transit compared with the transit in the fasted state. The scintigraphic images showed that in the pre-feed regimen, faster small intestinal transit resulted in disintegration of the enteric beads in the distal regions of the small intestine compared to fasting conditions where drug release occurred in the proximal small intestine. This acceleration may limit absorption of those drugs that are preferably absorbed in the upper gastrointestinal tract (Digenis et al., 1990). This pre-feed acceleration in small intestinal transit and propulsion of the dosage form was explored further by Fadda et al. (2009), where gastric emptying of tablets occurred before the arrival of food to the stomach in 60% subjects and small intestinal transit time in those subjects was found to be significantly shorter (100 min) than that observed in the standard fasted (204 min) and fed regimen (210 min).

Before entering the colon, both single-unit and multiple-unit dosage forms accumulate and stagnate at the ileocaecal junction for a variable period of time, (Wilding, 1995; Abrahamsson et al., 1996; Wilding et al., 2001). Interestingly, this stagnation of dosage forms was found to be affected by the meal size (Khosla et al., 1989) but no differences were observed when the meal composition was changed (Price et al., 1993). Multiple-unit dosage forms have been shown to have a longer colonic transit time than single-units (Fig. 1) (Follonier and Doelker, 1992; Abrahamsson et al., 1996). Gamma scintigraphy imaging taken after simultaneous administration of single- (tablet) and multiple-unit (pellets compressed as a tablet) formulations showed the tablet moving ahead of the pellets in the colon (Davis et al., 1984b). Furthermore, after intake, pellets have been found to be dispersed in the colon, mainly in the ascending colon (up to 14 h) and transverse colon (up to 48 h), whereas transit through distal parts was relatively fast (Abrahamsson et al., 1996). Dosing time was found to affect total gastrointestinal transit of non-disintegrating tablets (Oros®) (Sathyan et al., 2000). Morning dosing was found to result in the tablet being excreted the next morning (24 h total transit time). However, with the night dosing it is likely that the tablet is still in the proximal colon the morning after administration, delaying the tablet excretion to the following morning (36 h). This can be related to the pattern of bowel movement (Coupe et al., 1992b). In contrast, it was recently observed that after morning dosing, pellets were still present in the large intestine 5 days after administration (Basit et al., 2009).

Gender differences were also observed in gastrointestinal transit of radiopaque markers; gastric emptying, small-bowel transit and colonic transit were found to be significantly slower in female healthy subjects compared to males (Metcalf et al., 1987; Sadik et al., 2003). Colonic transit was also found to be delayed in elderly subjects compared to children and young adults (Stephen et al., 1986). These differences may also be expected in the transit time of modified-release dosage forms.

Gastrointestinal transit can differ in the diseased gut compared to healthy individuals. Patients with irritable bowel syndrome often have accelerated intestinal transit, particularly through the proximal colon (Vassallo et al., 1992). Patients with active ulcerative colitis have also been found to have significantly faster small intestinal transit (Davis et al., 1991) and colonic transit than controls (Hebden et al., 2000), contradicting results obtained by others (Hardy et al., 1987). It has been reported that many patients that underwent an ileocaecal resection (Munkholm et al., 1993) showed a shorter dosage form stagnation at the ileocaecal junction, thereby reducing the overall small intestinal transit time (Fallingborg et al., 1998). Other conditions of the gut like peptic and duodenal ulcers and gastroesophageal reflux disease also affect gastrointestinal transit (Maddern et al., 1985).

It is also possible to manipulate gastrointestinal transit through pharmacological means. Prokinetic drugs such as itopride, domperidone, velusetrag (TD-5108) and tegaserod are known to increase gastrointestinal motility (Degen et al., 2005; Manini et al., 2010). Concomitant administration of prokinetic drugs with modified-release dosage forms may result in a faster transit of the dosage forms, consequently limiting the *in vivo* performance of such systems. In addition excipients also modify gastrointestinal transit. For example, mucoadhesive polymers are believed to have a slower passage through the gut (Varum et al., 2008), while excipients, such as polyethylene glycol 400 (Basit et al., 2001; Schulze et al., 2003; Ashiru et al., 2008), sorbitol (Chen et al., 2007), mannitol (Adkin et al., 1995) and sodium acid pyrophosphate (Koch et al., 1993) have been shown to reduce small intestinal transit time, primarily due to stimulation of gastrointestinal motility.

3. Trends in modified-release dosage form transit and pharmacokinetics: *in vivo* case studies

The high variability in gastrointestinal transit presents significant implications for the *in vivo* performance of modified-release systems, either intended for delayed or sustained drug release. It is generally assumed that drug bioavailability from modified-release multiple-unit dosage forms is less variable compared to single-unit systems (Follonier and Doelker, 1992). An additional advantage of multiple-units is the lower risk of dose dumping, which is particularly relevant for sustained-release formulations where the drug is present at high loads (Efentakis et al., 2000). This different *in vivo* behaviour has been often associated with different gastrointestinal transit patterns of modified-release dosage

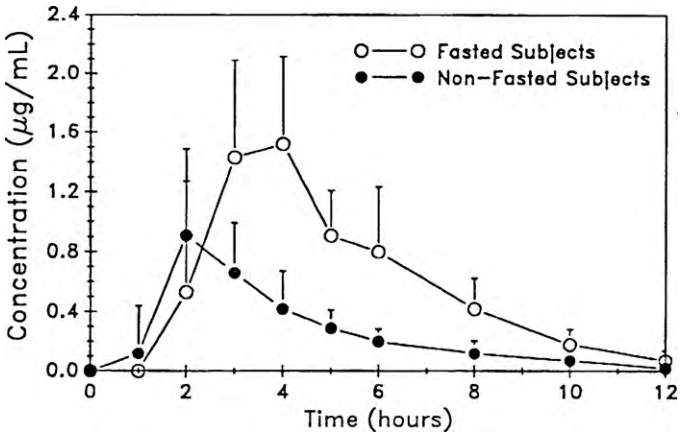

Fig. 4. Mean (+SD) plasma concentrations of erythromycin from enteric-coated pellets following single 250 mg oral doses under fasted and non-fasted (30 min pre-feed) conditions (Digenis et al., 1990).

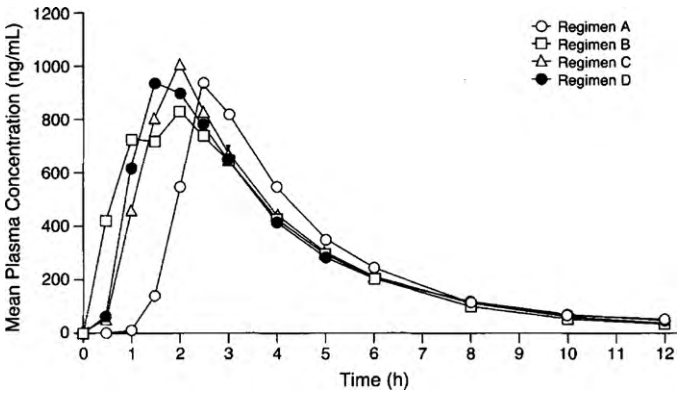

Fig. 5. Mean plasma lansoprazole concentrations after administration of enteric-coated granules with orange juice (regimen A), tomato juice (regimen B), strained pears (regimen C), or as an intact capsule (regimen D), $n = 20$ (Chun et al., 2002).

forms. The residence time of a dosage form in a specific region of the gastrointestinal tract is particularly relevant for those drugs that present a narrow "absorption window" (Davis, 2005). The residence time should be sufficient to allow complete drug release and absorption. How transit affects the behaviour of dosage forms is debatable; here we present a series of case studies highlighting the complex issue of transit, drug release and pharmacokinetics. Each example shows that gastrointestinal transit has a clear influence on the behaviour of such dosage forms, and includes some additional evidence for and against single-unit and multiple-unit formulations.

3.1. Delayed-release formulations

3.1.1. A comparison of single-unit and multiple-unit formulations in the fasted and fed states

In the fasted state, the extent of acetylsalicylic acid absorption, represented as area under the curve (AUC), was found to be significantly higher from enteric-coated tablets (7136.3 ± 2272.7 μmol h/L) compared to enteric-coated granules (5718.7 ± 1444.1 μmol h/L). However, the granules showed a lower intra- and inter-subject variability and a more uniform plasma level over 12 h (Fig. 3) (Edgar et al., 1984). Studies based on pharmacokinetics alone have also demonstrated greater predictability and reproducibility of the plasma profile of enteric-coated multiple-unit dosage forms compared to single-units (Green, 1966; Bechgaard and Nielsen, 1978; Bechgaard et al., 1982). In the case of didanosine, for example, enteric-coated beads (Videx®) have shown a lower variability in bioavailability compared to enteric-coated tablets and a faster onset of absorption (shorter t_{max}). This information led to the clinical development and subsequent commercialization of the didanosine enteric-coated granule preparation and the discontinuation of the enteric-coated tablet formulation (Damle et al., 2002a, Damle et al., 2002b). However, when food is introduced into the dosing scenario, the results can become more complex.

Pharmacokinetic variability was reduced for erythromycin enteric-coated pellets compared to enteric-coated single-units, after food intake (Graffner et al., 1986). The pellets, which were administered in a capsule, had higher bioavailability (AUC: 5.8 ± 0.4 mg h/L) compared to the tablet (AUC 3.9 ± 0.7 mg h/L). This low bioavailability and poor reproducibility with the single-unit can be attributed in part to the fact that six volunteers (out of 12) in this study had no measurable drug levels in blood up to 12 h post-administration. Delayed gastric emptying of the single-unit formulation in those volunteers is likely to have occurred due to the presence of food and subsequent meals (lunch and snack) that may have further hindered gastric emptying. It should be also borne in mind that differences observed in drug absorption from enteric-coated delayed-release formulations may also be due to variability in gastrointestinal pH in addition to variability in transit (Fallingborg et al., 1989).

3.1.2. Feeding regimen can affect transit, which in turn can influence drug release from enteric-coated systems

Commonly, only two feeding regimens have been considered in gastrointestinal transit and bioavailability studies: fasted and fed and these were discussed previously. Digenis et al. (1990) designed a pharmacoscintigraphic study introducing a different feeding regimen: dosage form administration 30 min before food intake (pre-feed). Peak plasma concentration of erythromycin was achieved earlier under the pre-feed regimen, when compared to the fasted state (Fig. 4). However, oral drug bioavailability (AUC: 3.17 vs. 7.29 μg h/ml) was lower in the pre-feed regimen. A higher inter-individual variability was also noticed when pellets were administered in the fasted state.

After food intake, gastric pH rises to 5–5.5 and enteric-coatings can start to dissolve or soften depending on the pH threshold of the polymer and this may explain the faster disintegration of the pellets under pre-feed conditions. However, a shorter residence time in the small intestine (148 ± 60 min vs. 207 ± 46 min) may also have contributed to the lower drug bioavailability in non-fasting conditions as erythromycin is preferably absorbed in the small intestine. This faster transit through the small intestine was attributed to the stimulation of intestinal motility by the ingestion of food. However, a complicating factor in this case is that erythromycin also has prokinetic activity, hence gastric and duodenal motility could have been stimulated (Digenis et al., 1990). However, Fadda et al. (2009) also reported faster small intestinal transit in the pre-feed regimen for non-disintegrating placebo tablets, ruling out a pharmacological effect and highlighting a food effect on gut physiology. Peristaltic activity and intestinal flow have been shown to increase after food intake, which may have contributed to the results obtained (Matuchansky et al., 1972; Kerlin et al., 1982).

3.1.3. The type of food or drink may affect the onset of absorption from enteric-coated dosage forms

Bioequivalence of lansoprazole enteric-coated granules was investigated in healthy volunteers in the presence of different juices (orange juice, tomato juice, or a small amount of strained pears). The bioavailability of lansoprazole was similar in all cases (Fig. 5), however, the onset of drug absorption was significantly delayed with orange juice compared to the other juices and control, result-

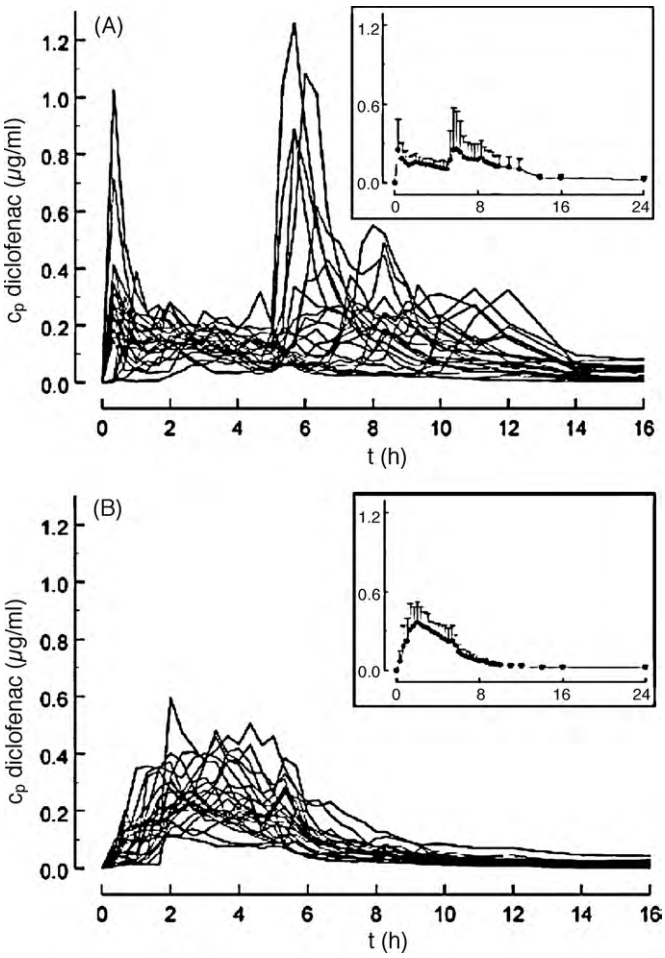

Fig. 6. Individual and mean (box) diclofenac plasma concentration profiles ($n = 24$) obtained after administration of 100 mg diclofenac in the form of (A) sustained-release tablets and (B) sustained-release pellets in fasting conditions (Garbacz et al., 2008).

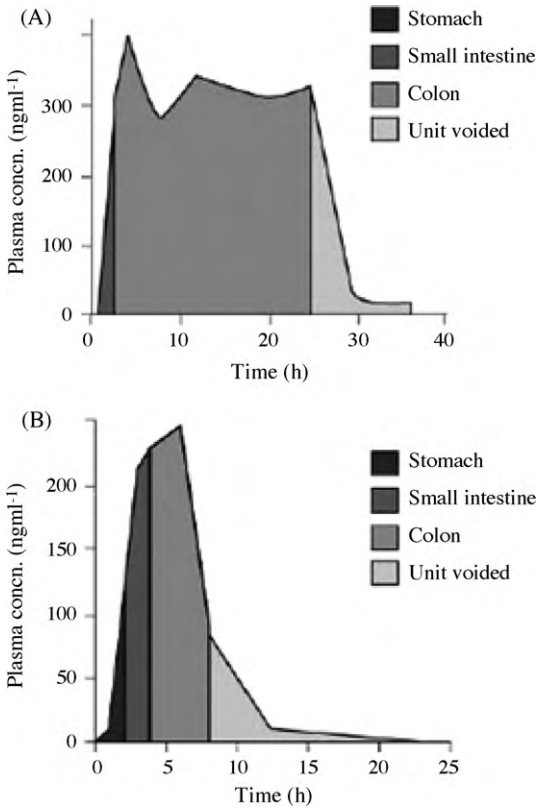

Fig. 7. Plasma concentration-time profiles of oxprenolol delivered from an OROS® system in a volunteer with (A) long and (B) short colonic transit (Wilson and Washington, 1988).

ing in a later t_{max} (3 h vs. 1.7 h in control) (Chun et al., 2002). This may be related to differences in gastric emptying of the liquids, as orange juice is known to have a slower rate of emptying compared to tomato juice possibly because of the lower pH of orange juice (Haggard and Greenberg, 1941). Low pH liquids are known to have a slower rate of gastric clearance (Rasmussen et al., 1999; Chaw et al., 2001). It is not clear if such an observation would occur with single-units.

3.2. Sustained-release formulations

3.2.1. A comparison of single-unit and multiple-unit formulations in the fasted and fed states

In a recent study in fasted volunteers, a large inter-subject variability in diclofenac plasma profiles was observed after administration of a sustained-release matrix tablet, with presence of multiple absorption peaks (Fig. 6). This was not observed when the drug was administered as sustained-release multiple-units (pellets). It was suggested that the single-units were more sensitive to physical stress, specifically during passage through the pyloric sphincter and ileocaecal junction (Garbacz et al., 2008).

The oral bioavailability of oxprenolol delivered by the OROS® sustained-release system was demonstrated to be highly variable and dependent on intestinal transit time (Fig. 7). In the example shown, one subject voided the dosage form after 24 h whereas a different subject excreted the dosage form at around 8 h, resulting in a much lower drug bioavailability (Wilson and Washington, 1988).

Sustained-release tablets showed a much higher inter-subject variability than sustained-release granules in the fed state (Delhotal-Landes et al., 1988). In a separate study, food intake did not affect theophylline bioavailability from sustained-release tablets (Sips et al., 1984). A tramadol multiple-unit formulation showed a reduced inter-and intra-subject variability in both rate and extent of drug absorption compared to a standard single-unit dosage form in healthy volunteers after food intake. Besides similar drug bioavailability, a later t_{max} and a lower C_{max} was observed with the pellets. Also, food did not affect drug bioavailability from the sustained-release multiple-unit formulation (Cnota et al., 2005).

However, food intake resulted in a shorter t_{max} and higher C_{max} of verapamil delivered as sustained-release ethylcellulose-coated pellets with similar overall bioavailability to the fasted state. This may be argued to be due to the increased residence time in the upper gastrointestinal tract and consequent exposure to the available fluid (Marvola et al., 1989). When compared to the single-unit verapamil tablet, shorter t_{max} was achieved for the pellet formulation, both in fasted and fed states.

A pharmacoscintigraphic study demonstrated that a modified-release dosage form of diltiazem (four 7 mm mini tablets enclosed in a capsule) administrated in the fasted state disintegrated completely in the large bowel, providing sustained drug release and uniform absorption through the gastrointestinal tract. In contrast, administration after a high fat breakfast resulted in a prolonged gastric retention and tablet disintegration in the stomach in six out of eight volunteers. Thus, sustained-release properties of mini tablets were compromised after food intake resulting in dose dumping. This resulted in higher C_{max}, however the overall diltiazem bioavailability was not affected (Fig. 8) (Wilding et al., 1995).

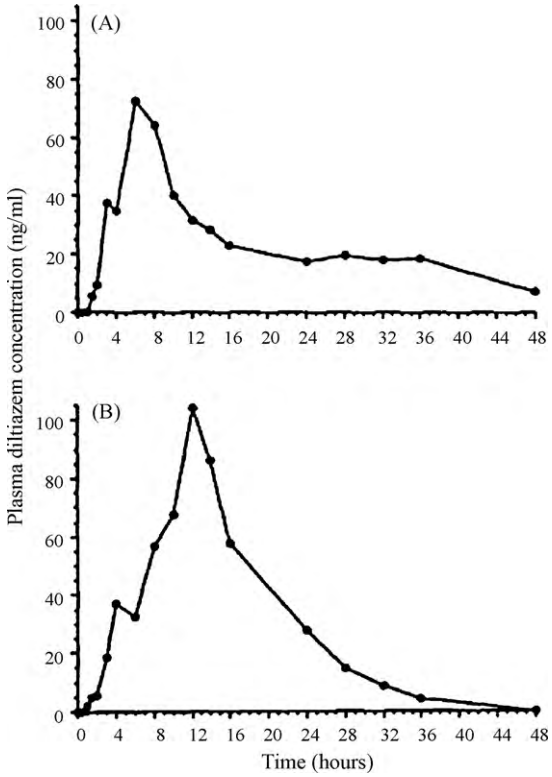

Fig. 8. Pharmacokinetic profile of diltiazem after oral administration of mini tablets in (A) fasted and (B) fed state in one subject (Wilding et al., 1995).

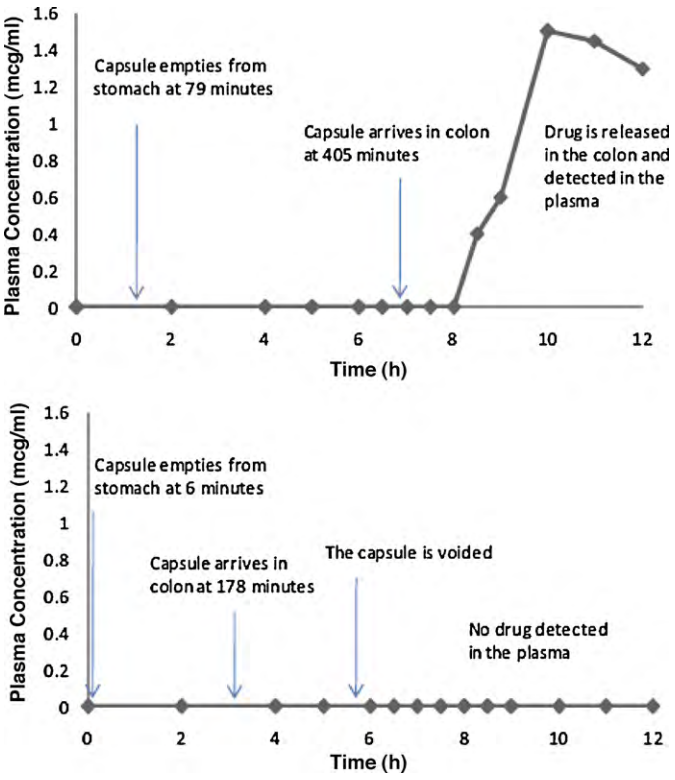

Fig. 9. Plasma profiles for 4-aminosalicylic acid delivered from a coated capsule designed to target the colon in two different volunteers (McConnell et al., 2008a).

3.2.2. *Potential for improved bioavailability from sustained-release pellets*

Metformin sustained-release coated pellets (EUDRAGIT L30D-55/NE30D) administered in the fasted state exhibited a lower C_{max} and later t_{max} when compared to single-units, however a relative bioavailability of 165% was achieved for the pellet formulation (Hu et al., 2006). The longer residence time and spreading of pellets along the small intestine may have contributed to the higher drug bioavailability observed, as metformin is mainly absorbed from the small intestine (Marathe et al., 2000). However, information on the transit of these formulations through the gastrointestinal tract was not provided.

3.3. *Site-specific drug delivery*

3.3.1. *A comparison of single-unit and multiple-unit formulations in the fasted and fed states*

Inter-subject variability was observed for delayed-release single-unit systems intended to deliver drugs to the ileo-colonic region of the gastrointestinal tract. In one individual, 4-aminosalicylic acid was detected in plasma at 8.5 h after administration of a coated capsule (colonic arrival of the formulation was 7 h), however, in a different subject colonic arrival was 3 h and the unit was voided at 6 h with no drug being released (Fig. 9) (Tuleu et al., 2002; McConnell et al., 2008a). This high inter-subject variability was also observed for EUDRAGIT S coated tablets, which have been observed to disintegrate at variable positions in the gastrointestinal tract and in some instances tablets were voided intact both in the fasted (Ibekwe et al., 2006) and in the fed state (Ibekwe et al., 2008b).

Coupling pharmacokinetic profiles and gamma scintigraphy imaging has shown that enteric-coated 5-aminosalicylic acid micropellets exhibited a shorter t_{max} (5.4 ± 1.2 h vs. 8.3 ± 1.6 h) and a higher C_{max} (2026 ± 1508 ng/ml vs. 1591 ± 1265 ng/ml) compared to the single-unit counterparts in the fasted state, however drug bioavailability was not statistically different (Wilding et al., 2003). Faster gastric emptying was observed for tablets (0.52 ± 0.36 h vs. $t_{50\%}$ 1.28 ± 1.10 h), but the gradual gastric emptying and consequent spreading of micropellets along the small intestine may have contributed to the gradual mesalazine release when the pH threshold was reached (terminal ileum and ascending colon).

However, McConnell et al. showed in a recent study that a pH-triggered system (pellets coated with EUDRAGIT S) had a premature release in the small intestine. Surprisingly, this system also failed to disintegrate in one subject. These findings contrast to those observed with a bacteria-triggered system (pellets coated with a biodegradable amylose and ethylcellulose layer) which released the drug once in the colon. Furthermore, pH-responsive pellets exhibited a shorter t_{max} (5–9 h) and a higher C_{max} (3.3 μg/ml) with higher inter-subject variability compared to the bacteria-trigger system (8–10 h, 2.1 μg/ml) (McConnell et al., 2008b).

By combining the two trigger mechanisms referred above (pH and bacteria), an effective and robust colonic delivery platform was successfully developed for single-unit dosage forms (8 mm tablets). Furthermore, tablet disintegration occurred in the ileocaecal junction or in the large intestine under different feeding conditions (fasted, fed and pre-feed) (Ibekwe et al., 2008a). This highlights the complexity of oral drug delivery where a multitude of factors are in play, namely, the gut physiology (pH, fluid content, bacteria levels, motility) the type of dosage form and underlying drug release mechanisms. In the latter examples, the trigger mechanism seems to be more important than the dosage form delivery system. This is even more critical for delayed-release formulations, particularly those intended for colonic delivery as the "release window" is narrower.

Different food effects were observed for two budesonide colonic delivery formulations. Budesonide controlled release pellets (Entocort®) administered as a capsule produced a significantly

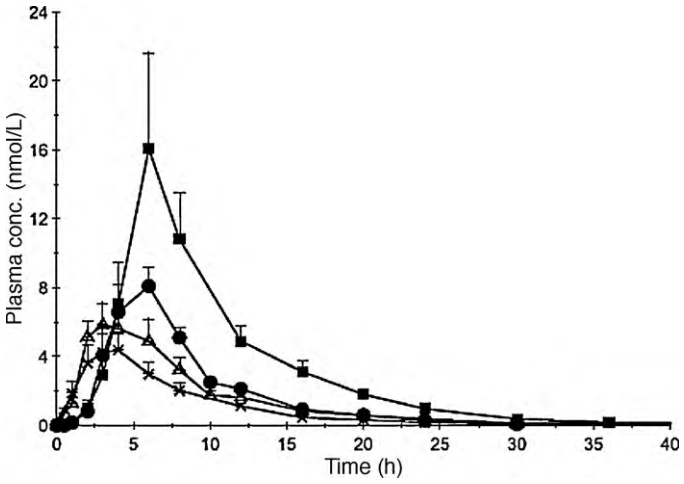

Fig. 10. Mean plasma concentration of budesonide after oral administration of controlled release capsule containing pellets to (■) fed Crohn's disease patients, (●) fed healthy subjects, (Δ) fasted healthy subjects and (x) immediate release capsules in fed patients (Edsbäcker et al., 2003).

higher C_{max} and a later t_{max} when administered after food intake (Edsbäcker et al., 2003) (Fig. 10). However, a different effect on budesonide absorption was observed when a high fat and high caloric breakfast was taken before administration of a new colonic drug delivery system using the MMX® technology. Food intake resulted in a lower rate and extent of absorption. Food–drug interaction or increased pre-systemic metabolism may have contributed to the lower bioavailability in the fed state (Brunner et al., 2005).

3.3.2. Disease can affect ileo-colonic transit and delivery

As should be apparent from the above case studies, the *in vivo* performance of modified-release dosage forms is complex and not always completely understood. Even less understood is the behaviour of formulations in the diseased gut. In subjects with colonic disease, gastrointestinal parameters, for example, transit time, fluid volumes, pH and microbiota have been reported to be different from healthy subjects (McConnell et al., 2008a).

Gastric emptying, small intestine transit time and drug bioavailability after administration of enteric-coated delayed-release 5-aminosalicylic acid tablets were reported to be similar for healthy volunteers and patients suffering from inflammatory bowel disease (both ulcerative colitis and Crohn's disease). In contrast, colonic transit has been shown to be significantly faster in patients with active ulcerative colitis than in healthy subjects (Hardy et al., 1987; Larouche et al., 1995).

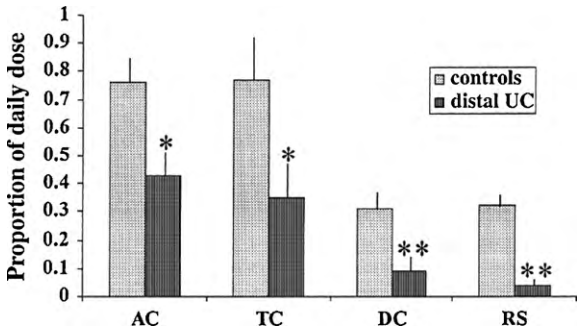

Fig. 11. Proportion of ^{111}In-labeled resin in four different regions of the colon (AC, ascending; TC, transverse; DC, distal; RS, rectosigmoid colon) after oral administration of a EUDRAGIT S coated capsule following 4 days of dosing in healthy volunteers (controls) and in patients with active distal colitis (distal UC) (Hebden et al., 2000).

A marked asymmetry in the distribution of amberlite resin was observed in the large intestine in healthy volunteers, with 69% in the proximal colon and 31% in the distal colon. Active left-sided ulcerative colitis patients showed a sharper asymmetry, with 91% of the material being found in the proximal colon compared to 9% in the distal colon (Fig. 11). This was correlated with faster transit in the distal colon in ulcerative colitis patients (mean 3.1 h) than in healthy subjects (mean 15.0 h). Thus, the distal colon is poorly exposed to the administered drug, which is further exaggerated in left-sided ulcerative colitis patients, compromising the efficacy of modified-release dosage forms in active disease (Hebden et al., 2000).

Higher budesonide bioavailability was observed in Crohn's disease patients compared to healthy volunteers, when administered as controlled release pellets (Fig. 10). Gastrointestinal transit imaging showed longer gastric emptying in Crohn's disease subjects than in healthy controls. However, pellet transit time through the ascending colon was shorter for Crohn's disease patients. It was also observed that budesonide was less well absorbed in the distal segments of the colon in healthy subjects (1.9%) when compared to the disease situation (26.2%), which may explain the higher bioavailability in Crohn's disease patients (Edsbäcker et al., 2003). Another study demonstrated that orocaecal transit time of sustained-release mesalazine multiple-units (lactulose H_2-breath test) was delayed in patients with active Crohn's disease. Furthermore, transit was longer in patients with an ileal or ileo-colonic inflammatory localization than in those with colonic regional disease (Tursi et al., 2003). This is particularly relevant when time-dependent modified-release dosage forms are designed with the intention of targeting the lower gut.

4. Conclusion

The process of gastrointestinal transit is complex, not least when it comes to the movement of modified-release dosage forms. In this review we have highlighted aspects of multiple-unit transit, the reliance on gastric emptying, the potential "stop–start" transit through the intestine and spreading through the colon. For instance, the differences in gastrointestinal transit of multiple-units and single-units come with some commonly held beliefs, such as the provision of better and more reproducible *in vivo* behaviour of the multiple-units. These were discussed in detail with reference to case studies. Multiple-unit dosage forms were generally shown to have a more predictable and reproducible gastrointestinal transit, which is then reflected in a lower inter-and intra-subject variability in oral bioavailability, particularly for delayed-release formulations. However, some generally accepted assumptions may be misleading when intra- and inter-individual variability is factored in. Furthermore, food intake and its caloric value, dosing times, age and disease situations add an extra level of uncertainty. There is still much to be improved upon, both in our understanding of the GI tract and its functionality, and in the development of new dosing systems.

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