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Review

The transit of dosage forms through the small intestine

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ABSTRACT

The human small intestine, with its enormous absorptive surface area, is invariably the principal site of drug absorption. Hence, the residence time of a dosage form in this part of the gut can have a great influence on the absorption of the contained drug. Various methods have been employed to monitor the gastrointestinal transit of pharmaceutical dosage forms, but the use of gamma-scintigraphy has superceded all the other methods. However, careful consideration of the time interval for image acquisition and proper analysis of the scintigraphic data are important for obtaining reliable results. Most studies reported the mean small intestinal transit time of various dosage forms to be about 3–4 h, being closely similar to that of food and water. The value does not appear to be influenced by their physical state nor the presence of food, but the timing of food intake following administration of the dosage forms can influence the small intestinal transit time. While the mean small intestinal transit time is quite consistent among dosage forms and studies, individual values can vary widely. There are differing opinions regarding the effect of density and size of dosage forms on their small intestinal transit properties. Some common excipients employed in pharmaceutical formulations can affect the small intestinal transit and drug absorption. There is currently a lack of studies regarding the effects of excipients, as well as the timing of food intake on the small intestinal transit of dosage forms and drug absorption.

Contents

1. Introduction

The human gastrointestinal tract can be divided into three distinct sections, namely the stomach, small intestine and colon. Each has its own physiological function and is varied in terms of pH, nature of its luminal contents, length and surface area as well as the presence of drug transporter systems (e.g. P-glycoprotein) (Mouly and Paine, 2003) and drug metabolising enzymes (e.g. CYP3A4) (Thummel et al., 1997). All these variables may singly or in combination influence the absorption of drugs.

The stomach, with its small surface area is a secretory rather than an absorptive organ, while the colon, which also has a relatively small absorptive area, usually plays a smaller role in drug absorption. Although some drugs, for example theophylline (Staib et al., 1986) and metoprolol (Godbillon et al., 1985) have been shown to be well absorbed in the colon, in general, absorption from this part of the intestine is incomplete and erratic (Koch-Weser and Schechter, 1981), since transit times through the colon are highly variable (Metcalf et al., 1987) ranging from less than an hour to more than 60 h (Hardy et al., 1985, 1987). Absorption from the distal part can be considered negligible since any remaining drug will be embedded in semi-solid faecal matter (Hirtz, 1984).

In comparison, the small intestine has an enormous absorptive area between 200 m^2 and 500 m^2 (Davenport, 1977) and is

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Table 1
A comparison of the mean small intestinal transit values obtained using different monitoring techniques.

Reference	Method	Dosage type	Mean small intestinal transit times (h)	
			Fasted	Fed
Evans et al. (1988)	Radiotelemetry	Single unit	5.7 (2.0)	–
Fallingborg et al. (1989)	Radiotelemetry with fluoroscopy (X-ray)	Single unit	8.0[a]	–
Billa et al. (2000)	Gamma-scintigraphy	Single unit	3.1 (0.7)	3.2 (0.4)
Coupe et al. (1991)	Gamma-scintigraphy	Single unit	–	3.0 (1.1)
Coupe et al. (1991)	Gamma-scintigraphy	Pellets	–	3.5 (1.0)
Yuen et al. (1993)	Gamma-scintigraphy	Pellets	4.2 (2.9)	3.9 (2.4)
Peh and Yuen (1996)	Marker drugs	Pellets	5.1 (2.0)	6.0 (2.3)

Bracket = standard deviation.
[a] Median value (range 2.8–14.0 h).

invariably the principal site of drug absorption (Koch-Weser and Schechter, 1981). Hence, the transit time or residence time of a dosage form in the small intestine can greatly influence the absorption of the contained drug, particularly if it is formulated as a modified released preparation or when the drug has poor aqueous solubility/dissolution.

2. Methods used in small intestinal transit studies

An understanding of the various methods that have been employed to determine the small intestinal transit time is helpful as different methods can yield different transit time values. Methods that have been used include X-ray imaging, radiotelemetry, magnetic moment imaging, gamma-scintigraphy as well as indirect methods, such as hydrogen breath test and the use of marker compounds that are site-specific in their absorption. Each method has its advantages and disadvantages.

X-ray imaging has not gained much popularity because of its potential radiation hazards which severely limit the number of images that can be taken and hence affecting the accuracy of the method. Moreover, the incorporation of high-density radio-opaque materials may alter the physical characteristics of the dosage form (Daly et al., 1982).

The radiotelemetry method employs a pH-sensitive radiotransmitting reusable capsule, originally designed to measure the pH profile of the gastrointestinal tract. Signals from the capsule are detected via a portable solid state receiver. A sharp rise in recorded pH signifies emptying of the capsule from the stomach into the small intestine. Thereafter, the position of the capsule in the abdomen is determined to be where the maximum signal strength of the transmission is detected by the receiver. The position is then recorded on a body map divided into nine sections over the abdomen. The capsule is deemed to have arrived in the caecum when its position is found to be in the right iliac fossa (Evans et al., 1988). Given that no visualisation of the capsule is available, it can be difficult to identify the exact location of the capsule in the small intestine or colon. Fallingborg et al. (1989, 1990) have combined the use of X-ray examinations to locate the capsule in the small intestine and colon, but the accuracy in determining the caecal transit is affected by the frequency in which images are captured. Moreover, the method is not readily applicable for monitoring the transit of actual pharmaceutical dosage forms. Instead of pH-sensitive, pressure-sensitive radiotelemetering capsule has also been used (Waller, 1975). Pressure values transmitted from the capsule are used to determine the location of the capsule in the gut based on distinct pressure patterns in the stomach, jejunum, ileum and colon.

The hydrogen breath test method entails co-administration of a non-absorbable disaccharide, namely lactulose. This compound is fermented by colonic bacteria to yield hydrogen gas, which can then be used to indicate arrival at the caecum when its concentration in the breath rises. However, lactulose is a physiological stimulant and has been shown to shorten the normal small intestinal transit time (Read et al., 1982). Also, an overgrowth of colonic bacteria in the small intestine may yield erroneous results. Moreover, this method is more suitable for estimating the orocaecal transit time rather than the small intestinal transit time, since gastric emptying cannot be determined using this method.

Use of marker drugs such as paracetamol and sulphasalazine relies on the fact that they are preferentially absorbed at specific sites of the gut. Paracetamol is preferentially absorbed in the small intestine and hence the rate at which it appears in the blood can be used as a measure of the gastric emptying (Heading et al., 1973; Clements et al., 1978). On the other hand, sulphasalazine is hydrolysed to sulphapyridine in the large bowel and measurement of the latter in the plasma can be used to determine the orocaecal transit time (Kennedy et al., 1979). Used in combination, the small intestinal transit time can be estimated from the difference of the gastric emptying time and the orocaecal transit time. Peh and Yuen (1996) have utilised these two compounds to study the gastrointestinal transit of pellets. However, the small intestinal transit times obtained were longer than those reported using gamma-scintigraphy with pellets of similar density and size range (see Table 1).

Casey et al. (1976) and Alpsten et al. (1976) were among the first to describe the use of gamma-scintigraphy for studying the in vivo fate of pharmaceuticals. Since then, this imaging technique has superceded all other methods in gastrointestinal transit studies of dosage forms. It is non-invasive, only exposes the study subject to low radiation doses and provides information on a continuous and quantitative basis. This allows complete characterisation of the gastric emptying and intestinal transit processes. Radiolabelling of the dosage forms can be achieved via incorporation of the radionuclide technetium-99m or indium-111 into the formulations. One can also incorporate a non-radioactive tracer, such as samarium-152 oxide or erbium-170 oxide followed by neutron activation of the final product (Davis et al., 1992). The location and transit process of the radiolabelled dosage forms after ingestion can be monitored continuously using a gamma-camera. Visualisation of the different regions of the gut could be easily achieved by giving a radiolabelled drink to the study subject. Employment of dual isotopes provides further refinement of the technique. Hence, the exact location of the dosage form within the different gut regions can be determined. Compared to the other methods, gamma-scintigraphy is thus more informative and more reliable for in vivo evaluation of dosage forms in the gastrointestinal tract.

Gamma-scintigraphy allows the different regions of interest (stomach and caecum) to be viewed continuously, and Podczeck et al. (1999) have pointed out the advantages of frequent imaging and illustrated that long time intervals between images can lead to limitations in the interpretation of the data. When monitoring liquids or multiparticulate dosage forms such as pellets, it is usual to record changes in radioactivity in the stomach and caecum at specified time intervals and the values are used to construct graphical

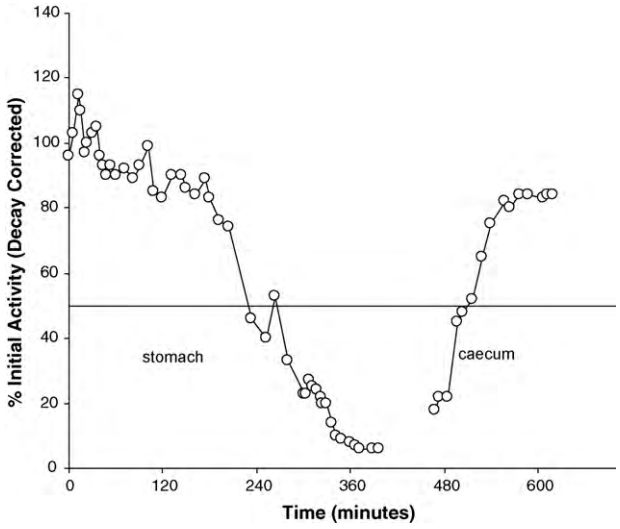

Fig. 1. Gastric emptying and caecal arrival profiles of pellets in a volunteer (adapted from Yuen, 1991).

presentation of the gastric emptying and caecal arrival processes as depicted in Fig. 1.

From the graphs, the time for 50% (t_{50}) of the test preparation to have emptied from the stomach or arrived in the caecum can then be determined. The small intestinal transit time is calculated accordingly, from substracting t_{50} for gastric emptying from t_{50} for caecal arrival. From the way the various parameters are calculated, it is clear that the accuracy of the values obtained will be affected by the intervals in which the scintigraphic images are captured. Moreover, if the gastric emptying or caecal arrival profiles are irregular, it may be difficult to determine the t_{50} value (as shown by the gastric emptying profile in Fig. 1). To circumvent these problems, Podczeck et al. (1995) have recommended the use of statistical moments for analysing the scintigraphic data to provide a more comprehensive description of the gastrointestinal transit processes. This approach has since been adopted in later studies (Basit et al., 2001, 2002; Schulze et al., 2003, 2005, 2006).

The gastric emptying or caecal arrival of a single unit non-disintegrating dosage form is a simple all or none process. Therefore, the interval in which the images are acquired is even more crucial for accurate estimation of the gastric emptying or caecal arrival time. For gastric emptying, Podczeck et al. (1999) have shown in their study that, to obtain reliable results, the maximum time interval between image acquisitions was 3 min for light ($1.50\,g\,cm^{-3}$) and 2 min for dense ($3.70\,g\,cm^{-3}$) tablets. Likewise, more frequent acquisitions at shorter time intervals during the caecal arrival process will permit a more reliable estimate of the caecal arrival time.

More recently, the use of magnetic moment imaging has also been used to determine the small intestinal transit of tablets (Weitschies et al., 2005). The dosage forms can be labelled by incorporating iron oxide (Fe_3O_4) and then magnetised using a permanent magnetic assembly. Their location in the gut is then determined externally using magnetic sensors. Weitschies et al. (2005) have used this method to determine the small intestinal transit of extended release tablets. They reported a mean small intestinal transit value of 3.2 h, which is in good agreement with the values obtained from some studies (Billa et al., 2000; Coupe et al., 1991) using gamma-scintigraphy. However, in a recent study using this technique, Goodman et al. (2010) reported a mean small intestinal transit value of more than 5.5 h for single unit tablets, which they suggested could be due to the large size ($19\,mm \times 6\,mm \times 9\,mm$) and density ($2.2\,g\,cm^{-3}$) of their tablets. They also acknowledged that, it was difficult to distinguish the ileocaecal junction from the ascending colon using this technique.

Schiller et al. (2005) have also reported the use of water-sensitive magnetic resonance imaging (MRI) to assess the intestinal transit of dosage forms. However, to be discriminative by MRI, the dosage forms have to contain water. Moreover, Schiller et al. (2005) reported that the non-disintegrating capsules used in their study could only be identified after suppression of intestinal motility with an intravenous injection of scopolamine hydrobromide. Thus, the small intestinal transit time obtained will not be reflective of the values under normal conditions.

Monitoring techniques such as impedance epigastrography (Sutton et al., 1985) and applied potential tomography (Avill et al., 1987) have also been described in the literature. However, both methods are suited for determining gastric emptying only, through detecting changes in gastric electrical impedance during the emptying process. They cannot be used for dosage forms other than liquids and semi-solids. Visualisation of tablets in the gastrointestinal tract using ultrasound has also been reported in the literature (Maublant et al., 1988), but the tablets could not be detected once they had entered the small intestine.

As pointed out earlier, different monitoring techniques may yield different small intestinal transit values. Table 1 gives a comparison of the small intestinal transit times of pellets and single unit dosage forms obtained from a few selected studies using different monitoring techniques to highlight the differences in transit values obtained.

It is evident from the comparison above that the radiotelemetry method tended to yield longer small intestinal transit values. This may be due to the problem in locating the exact position of the capsule via the radio signal, even when combined with X-ray imaging which was used in the study by Fallingborg et al. (1989).

In the case of the method employing marker drugs, a major difficulty is in estimating the gastric emptying profile of the pellets using paracetamol (Peh and Yuen, 1996). Firstly, the drug may leach out from the pellets in the stomach and empties unimpeded into the small intestine for absorption before actual emptying of pellets has occurred. Secondly, the profile for paracetamol absorption is not necessarily representative of that for pellet emptying. This is because the absorption of paracetamol is also influenced by its dissolution from the pellets, which in turn is influenced by the pellet formulation. A similar problem is also encountered in the estimation of the orocaecal transit time using sulphasalazine. While detection of sulphapyridine in plasma signals the arrival of the preparation in the colon, the caecal arrival profile of the pellets is difficult to be determined using the sulphapyridine plasma values. Thus, potential errors in estimating both the gastric emptying and the caecal arrival will affect the reliability of the method in estimating the small intestinal transit time.

3. Transit of pharmaceutical dosage forms in the small intestine

Most of our understanding and knowledge on the gastrointestinal transit behaviour of pharmaceutical dosage forms were largely derived from studies carried out in the 80s and 90s using gamma-scintigraphy. The influence of various factors such as dosage form variables, excipients and food on their transit behaviour has been investigated using the gamma-scintigraphic technique and they are discussed below.

3.1. Effect of dosage form variables

Oral dosage forms can be generally categorised as liquids or solids. The liquid type includes solutions, suspensions and emul-

sions, whereas solid dosage forms are represented by small pellets and single unit tablets. However, if the pellets or tablets are formulated to disintegrate and release the contained drug immediately after ingestion, then in theory, they will behave like solutions or suspensions in the gastrointestinal tract. On the other hand, some solid dosage forms, by virtue of their design, will remain intact throughout their passage in the gut. Examples are pellets coated with a non-destructable film, matrix tablets and osmotic pumps. It is of interest therefore, how these different preparations behave with regard to their residence or transit time in the small intestine.

In a paper published in 1986, Davis et al. (1986) presented a meta-analysis of data collected from 201 investigations on the gastrointestinal transit of various dosage forms using gamma-scintigraphy. Of these, 23 studies were on solutions, 82 on pellets and 96 on single units. The studies were conducted on young adult male volunteers and in some cases on elderly women. The dosage forms were administered with different amounts of food in the stomach, ranging from fasted state to a heavy English breakfast.

From the meta-analysis, it was deduced that, the transit of dosage forms through the small intestine is not influenced by their physical state (solutions, pellets or single units), or their size and shape, nor by the presence of food. Also, small intestinal transit was observed to be more consistent than gastric emptying, being in accord with the observations of other workers (Coupe et al., 1991; Yuen et al., 1993; Clarke et al., 1995). The authors concluded that the mean transit time through the small intestine was about 3–4 h.

Several later studies conducted on pellets or single unit tablets using gamma-scintigraphy also found the mean small intestinal transit times to be closed to 3–4 h. Coupe et al. (1991) reported a mean value of 3.5 ± 1.0 h with pellets administered after a light breakfast. Yuen et al. (1993) reported a mean value of 4.2 ± 2.9 h with pellets administered under fasted condition and 3.9 ± 2.4 h when administered after a meal. In another study (Davis et al., 1984), the small intestinal transit time of pellets after a light breakfast was not significantly different from that following a heavy breakfast. The reported mean transit values after the light and heavy breakfast were 3.1 ± 2.8 h and 3.4 ± 2.8 h, respectively. Kenyon et al. (1995) also studied the gastrointestinal transit and absorption of a novel sustained release tablet formulation of naproxen, which on administration, disintegrated to release discrete pellets which acted as individual sustained release units. Food was found to have no effect on the transit of the pellets and the mean small intestinal transit time under fasted condition was 3.7 ± 1.6 h and under fed condition was 3.2 ± 1.1 h.

For single unit systems, Maublant et al. (1987) have reported a mean small intestinal transit value of 4.1 ± 0.3 h for radiolabelled theophylline tablets when taken fasted. In another study, Coupe et al. (1991) reported a mean value of 3.0 ± 1.1 h when non-disintegrating tablets were given after a light breakfast, while Davis et al. (1984) reported a mean value of 3.2 ± 2.4 h for an osmotic device, which was also taken following a light breakfast. Almost similar values were obtained by Billa et al. (2000) who reported a mean value of 3.1 ± 0.7 h when the tablets were administered after an overnight fast and 3.2 ± 0.4 h when given after a standard meal.

From the data of the studies reviewed above, it can be seen that the small intestinal transit values were rather consistent among studies, regardless of the dosage forms used or whether they were dosed fed or fasted. Most studies reported a mean small intestinal transit time of about 3–4 h, which is also in good agreement with that reported for solid food, with a reported mean value of 4.0 ± 1.4 h (Read et al., 1986) and water with a reported mean value of 4.0 ± 0.8 h (Prokop et al., 1984). Christensen et al. (1985) also found no significant difference between the small intestinal transit times of a solution and a pellet formulation. The mean transit value for the solution was 4.1 ± 2.3 h and for the pellet formulation was 3.4 ± 4.1 h.

Clarke et al. (1995) studied the effect of density on gastrointestinal transit using pellets (1.18–1.40 mm in size) of 1.5 g cm^{-3}, 2.0 g cm^{-3} and 2.4 g cm^{-3} under fasted condition. No significant difference was observed in the small intestinal transit times of the three types of pellets. The mean small intestinal transit times of the three pellet formulations were 4.5 ± 1.4 h, 4.4 ± 1.4 h and 3.4 ± 1.1 h, respectively. The results are in accord with the findings of an earlier study by Devereux et al. (1990), where no significant difference was also observed between the small intestinal transit times of two pellet formulations with densities of 1.5 g cm^{-3} and 2.8 g cm^{-3} under both fed and fasted conditions. In contrast, density as well as size has been shown to prolong the small intestinal transit in another study by Clarke et al. (1993). The pellets sizes used in this study conducted under fasted condition were 0.5 mm and 4.75 mm, each with two densities of 1.5 g cm^{-3} and 2.6 g cm^{-3}. The mean small intestinal transit time of the 0.5 mm pellets showed a statistically significant increase from 2.7 ± 1.0 h to 3.1 ± 1.1 h when the density was increased. With the larger pellets, the mean transit time was increased from 3.2 ± 0.8 h to 4.0 ± 1.8 h with an increase in density, but the increase was not statistically significant, which may be attributed to the small number of volunteers used in the study ($n = 8$). When the data for size or density were pooled, the authors found that these two parameters showed a statistically significant effect in prolonging the small intestinal transit time of the pellets. A more recent study by Podczeck et al. (2007) conducted using tablets with 3.2 mm, 6.6 mm and 12.2 mm diameters and densities of 1.38 g cm^{-3} and 2.86 g cm^{-3}, also provided evidence that the small intestinal transit of the dense tablets was longer than the generally accepted values of 3–4 h.

From the results of these studies, it is clear that there is disagreement regarding the effect of density and size of dosage forms on the small intestinal transit. Therefore, more work is required to re-examine the effects of these two factors, especially using studies with larger number of subjects and careful consideration of interval used in image acquisition, as well as proper analysis of the scintigraphic data, such as using statistical moments proposed by Podczeck et al. (1995).

It should be noted that, individual small intestinal transit values appeared quite variable and the range quite big. From the data of the meta-analysis by Davis et al. (1986), the values can range from <1 h to about 6 h for single unit tablets, about 1–9 h for pellets, and 2–6 h for solutions. In a study in which six volunteers were repeatedly given an Indium-III labelled tablet together with a capsule of technetium-99m labelled pellets on four separate occasions, Coupe et al. (1991) also observed inter-subject variability to be larger than intra-subject variability. Thus, while the mean values reported were quite consistent among studies, one should also take cognizance of the high variability among individuals.

The gamma-scintigraphy method also allows the dispersion properties of multi-unit systems (pellets) in the small intestine to be determined. Yuen et al. (1993) observed that the pellets were well dispersed during transit along the small intestine, but the degree of dispersion was influenced by the gastric emptying rate of the pellets. When the pellets were emptied rapidly, less spreading was observed. However, when the pellets were emptied slowly and regularly into the small intestine, better dispersion was obtained as suggested by Davis et al. (1989).

While pellets have been observed to be well dispersed in the small intestine, they were also found to accumulate or regroup at the ileocaecal junction, prior to their entry into the caecum (Yuen, 1991; Coupe et al., 1991; Clarke et al., 1993). After a period of stagnation, the pellets were observed to empty into the caecum in boluses, often in rapid succession, resulting in a steep caecal arrival profile (as seen in Fig. 1). The scintigraphic images in Fig. 2 illustrate the caecal arrival and accumulation of pellets at the ileocaecal junction, followed by emptying in boluses into the caecum.

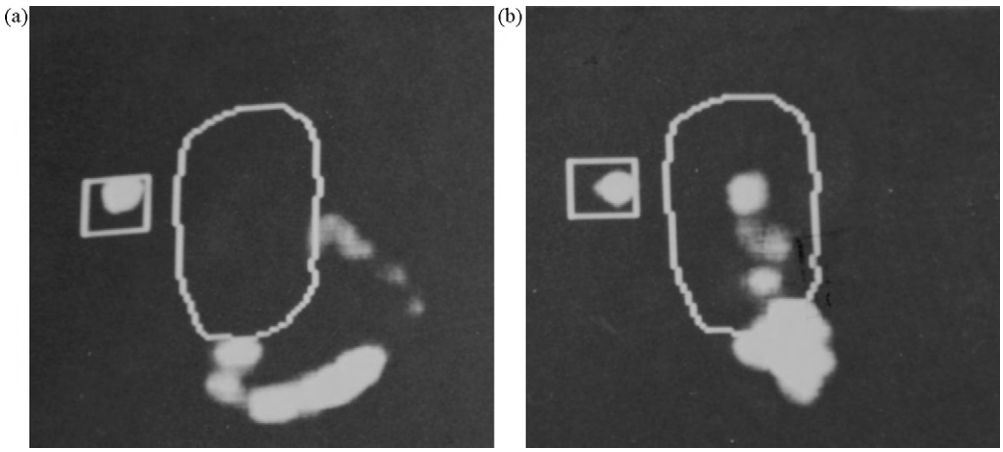

Fig. 2. Scintigraphic images showing (a) arrival of pellets at the ileocaecal junction and (b) accumulation of pellets at the junction followed by emptying in boluses into the caecum (taken from Yuen, 1991).

The phenomenon of stagnation at the ileocaecal junction has also been reported with single unit systems (Coupe et al., 1991; Podczeck et al., 2007). Thus, for both single unit and multiparticulate systems, such stagnation would lead to an extension of their transit time through the small intestine. Intake of a meal is known to increase peristaltic activity of the small intestine and induce a gastro-ileocaecal reflex, that initiates passage of fluids and solids through the ileocaecal junction (Schiller et al., 2005; Kerlin et al., 1982). Therefore, if this reflex is initiated during the stagnation period, it may lead to a shortening of the small intestinal transit time. Ingestion of food 45 min after administration of a tablet preparation has been reported to significantly reduce the small intestinal transit time, but the effect was more attributable to an increase in the intestinal peristaltic activity (Fadda et al., 2009). No study has yet been carried out to investigate the effect of food intake during the stagnation period on the small intestinal transit time.

3.2. Effect of excipients

There is a paucity of information regarding the effect of pharmaceutical excipients on the gastrointestinal transit of dosage forms. Only few studies have been reported in the literature and it is generally assumed that excipients, at the amounts used in drug formulations, do not have any effect on the small intestinal transit (Adkin et al., 1995a). However, there are studies which show that some excipients may indeed influence the small intestinal transit and absorption of drugs.

Lactulose, an unabsorbable disaccharide employed in the hydrogen breath test and used in the treatment of chronic constipation, has been shown to accelerate small intestinal transit (Read et al., 1980, 1982; Staniforth, 1989). Therefore, it is possible that other poorly or non-absorbable sugars (or their derivatives) such as sorbitol, xylitol and mannitol may have similar effects, especially when considerable amounts are used, for example as excipients in chewable and oral effervescent formulations.

Xylitol at a dose of 30 g (in 200 ml water) has been shown to accelerate small intestinal transit (Salminen et al., 1989) but its effect at lower doses remains to be studied. Mannitol, sucrose and sodium acid pyrophosphate (SAPP) commonly used exipients in chewable and effervescent formulations were investigated by Adkin et al. (1995a) in fasted healthy human volunteers. The excipients were administered at doses of 2.264 g, 4.08 g and 1.1 g, respectively, in 200 ml radiolabelled iso-osmotic solutions to the volunteers on separate occasions. The small intestinal transit times of the SAPP and mannitol solutions were found to be reduced by 39% and 34%, respectively, compared to purified water used as a control. Small intestinal transit of the sucrose solution was reported to be similar to the control. The mean small intestinal transit time for the control (water) was 4.0 ± 1.6 h, for SAPP solution 2.5 ± 0.8 h, for mannitol solution 2.6 ± 0.8 h and for sucrose solution 3.8 ± 0.6 h. In a separate communication, the same workers demonstrated that the effect of mannitol was concentration dependent (Adkin et al., 1995b) (see Table 2). Interestingly, the small intestinal transit times of five 6 mm diameter non-disintegrating tablets were not affected when co-administered with the SAPP and mannitol solutions in this study. The authors ascribed this to delayed gastric emptying of the tablets compared with the solutions. They observed that in many cases, the solutions moved ahead of the tablets in the small intestine and therefore the tablet transit was not influenced by the excipients in the solutions. The authors also suggested that the effect of SAPP

Table 2
Examples of excipients that have been shown to significantly affect small intestinal transit.

Excipients	Dose/preparation	% Reduction in small intestine transit time	Reference
Xylitol	30 g/200 ml water	NA	Salminen et al. (1989)
Mannitol	0.755 g/200 ml water	11	Adkin et al. (1995b)
	1.509 g/200 ml water	23	
	2.264 g/200 ml water	34	
Sodium acid pyrophosphate	1.1 g/200 ml water	39	Adkin et al. (1995a)
Sodium acid pyrophosphate	1.132 g/240 ml water	44	Koch et al. (1993)
Polyethylene glycol 400	10 g/150 ml orange juice	35	Basit et al. (2001)
Polyethylene glycol 400	10 g/150 ml orange juice	37	Basit et al. (2002)
Polyethylene glycol 400	1 g/150 ml water	9	Schulze et al. (2003)
	2.5 g/150 ml water	20	
	5 g/150 ml water	23	
Oleic acid	1.2 g (in two modified release capsules)	>45[a]	Dobson et al. (1999)

[a] Increase in small intestinal transit time of five co-administered non-disintegrating 6 mm tablets.

and mannitol is transitory and that the cathartic effect is due to the excipient's ability to increase the volume of fluid retained in the lumen. However, they reported that in subsequent studies (unpublished), mannitol was observed to accelerate the small intestinal transit of suspended cimetidine drug particles, resulting in reduced drug absorption. Thus, it appears that the effect of excipient on the transit and absorption of a drug (if any) depends on their proximity to one another in the intestine, which in turn is dependent on their physical state in the stomach (whether in solution, suspension or single unit). Due to differences in their rate of gastric emptying, they may transit separately in the small intestine as observed by Adkin et al. (1995a).

In an earlier study, Koch et al. (1993) observed that ranitidine absorption was markedly reduced when SAPP was used as an excipient in an efferverscent oral solution dosage form of the drug, compared to a conventional oral tablet. They observed that 1132 mg of SAPP used in the efferverscent formulation caused the small intestinal transit time to be reduced by 44%, which resulted in a decrease in the extent of ranitidine absorption. In this study, both the excipient and the drug were administered together in a solution and thus shared similar gastric emptying and small intestinal transit properties. This serves to support the suggestion that the proximity of excipient and drug in the gut is important for the excipient effect to take place.

In a study by Wilding et al. (1994), it was observed that non-aqueous suspensions of a drug-resinate formulated using fractionated coconut oil (Migylol™) had significantly shorter small intestinal transit times compared to aqueous suspensions, although they suggested that further work was required to establish the small intestinal cathartic effect of the excipient.

The influence of polyethylene glycol 400 (PEG 400), a commonly used solvent or cosolvent in pharmaceutical formulations, on gastrointestinal transit has also been investigated by Basit et al. (2001). The small intestinal transit time of a liquid preparation comprising 150 ml of orange juice was found to be reduced by 35%, when 10 g of PEG 400 was added into the preparation. However, the transit time of non-disintegrating pellets administered simultaneously with the liquid preparation was not significantly affected by the presence of PEG 400. The authors attributed the discrepancy to more rapid gastric emptying of the liquid preparation compared to the pellets. Therefore, the PEG containing liquid progressed ahead of the pellets in the small intestine and exerted no influence on the transit of the proceeding pellets. On the other hand, pellets that were emptied concurrently with the PEG 400-containing liquid from the stomach, were subjected to its influence and thus, explained the shorter average small intestinal transit time observed (though not statistically significant) when the pellets were administered with the PEG 400-containing liquid.

Using the same liquid preparation, Basit et al. (2002) in a subsequent study, demonstrated that the bioavailability of ranitidine from an immediate release pellet formulation was significantly reduced by 31%, when the pellets were administered with the PEG 400-containing liquid. Small intestinal transit time of the liquid was also significantly shortened by 37% by the presence of PEG 400, being consistent with that observed in the previous study. Although ranitidine was administered in the form of a solid pellet formulation, its rapid dissolution from the pellets would mean that the dissolved drug was in all likelihood, transported along with the liquid preparation. Since ranitidine is mainly absorbed from the small intestine, the accelerating effect of the PEG 400-containing liquid on small intestinal transi, caused the ranitidine bioavailability to be significantly reduced.

In another study, Schulze et al. (2003) attempted to study the effect of different concentrations of PEG 400 on the gastrointestinal transit and absorption of ranitidine. The volunteers were given on four separate occasions, 150 ml water containing 150 mg ranitidine and either 0 (control), 1 g, 2.5 g and 5 g PEG 400. There was no significant difference in gastric emptying of the different solutions, but the presence of 1 g, 2.5 g and 5 g PEG 400 was observed to reduce the small intestine transit time of the solutions by 9%, 20% and 23%, respectively, against the control. They concluded that low concentrations of PEG 400 enhance ranitidine absorption possibly via modulation of intestinal permeability, while high concentrations have a detrimental effect on the drug absorption presumably via reducing the small intestinal transit time.

The influence of PEG 400, propylene glycol, D-α-tocopheryl-polyethylene glycol-1000 succinate (TPGS) and Labrasol® on small intestinal transit and absorption of two model drugs, namely ampicillin and antipyrine has also been investigated using beagle dogs (Schulze et al., 2005). The doses of the excipients used were 1 g, 2 g, 1 g and 2 g, respectively, whereas the doses of ampicillin and antipyrine were 200 mg and 100 mg. At the doses used, the excipients were found to have limited influence on the small intestinal transit and absorption of the model drugs. The small intestinal transit and bioavailability data for the excipient treatment were not significantly different from using water as the control. In a later study using human volunteers (Schulze et al., 2006), the excipients propylene glycol, D-α-tocopheryl-polyethylene glycol-1000 succinate (VitE-TPGS) and glyceryl mono-8 dicaprate (Capmul MCM®), at a dose level of 5 g each were also found to have no appreciable or significant effect on the small intestinal transit time.

The presence of fat in the ileum has been shown to slow bulk transit in the small intestine via a physiological feedback mechanism known as the ileal brake (Spiller et al., 1984). It was postulated that this feedback mechanism allows remaining fat in the upper gut to be further digested and absorbed by slowing their transit through the small intestine. The effect of oleic acid on the ileal brake in relation to the transit of non-disintegrating tablets was investigated by Dobson et al. (1999). Three doses of oleic acid were used, namely 300 mg, 600 mg and 1200 mg. To target release in the ileum, the oleic acid was delivered in technetium-99m labelled modified release capsules, which can withstand disintegration in acidic media. The human volunteers were given the different doses of oleic acid, including one study phase with no oleic acid capsule (control) on four separate occasions. On each occasion, five non-disintegrating 6 mm tablets labelled with Indium-III were given together with the oleic acid capsules (or alone in the case of the control) and another five similar tablets labelled with technetium-99m 1 h later.

In the majority of volunteers, the small intestinal transit time of the tablets was reported to increase with oleic acid treatment. However, a statistically significant difference in small intestinal transit time was only observed with the Indium-III labelled tablets given together with 1200 mg of oleic acid, where the mean transit time was increased by more than 45% (from 3.6 ± 0.9 h to 5.3 ± 1.3 h). In general, the transit of the second set of tablets given 1 h later appeared to be less affected by oleic acid administration, thus contradicting the postulation that, the ileal brake slows the transit of the proceeding bulk materials in the small intestine. Wide inter-subject variation in response to the oleic acid treatment was also noted and this could be due to the oleic acid being not delivered to the correct site in the ileum. A major drawback of the study was that, the exact location where the oleic acid was released could not be determined. This was due to the presence of the technetium-99m labelled tablets in the images. Otherwise, a more meaningful interpretation of the data could have been obtained.

From these few studies reviewed, it is apparent that some excipients have the potential to influence the small intestinal transit of dosage forms and consequently the bioavailability of drugs. This is especially true if the excipients are used in larger amounts and therefore merits more work to be carried out in this area. A summary of the excipients that have been shown to affect small

intestinal transit and their relevant doses is given in Table 2 for easy reference.

3.3. Effect of timing of food intake

Many studies have shown that the small intestinal transit of various dosage forms (liquids or solids) is not affected by food (Davis et al., 1986; Devereux et al., 1990; Yuen et al., 1993; Kenyon et al., 1995; Billa et al., 2000). Moreover, their small intestinal transit times are in good agreement with that of solid food and water, thus supporting the suggestion by Hofmann et al. (1983) that drugs present as particulate dispersions or solutions, are propelled at the same rate as food particles along the small intestine.

Prolonged exercise was reported to significantly increase the gastric emptying rate of a solid meal but had no significant effect on the small bowel transit time (Cammack et al., 1982) and hence by extension, may not affect the small intestinal transit of pharmaceutical dosage forms. In contrast, psychological stress was observed to hasten the small intestinal transit of a standard meal and thus, may have a similar effect on pharmaceutical dosage forms.

In most studies investigating the effect of food on the small intestinal transit of pharmaceutical dosage forms, the preparations were usually administered immediately following a standard meal and compared to that administered after an overnight fast (Davis et al., 1986; Devereux et al., 1990; Yuen et al., 1993; Clarke et al., 1995; Billa et al., 2000). Thus, the effect of a meal given in between these two study conditions is little known. In a recent paper, Fadda et al. (2009) investigated how the timing of tablet and food administration could influence the small intestinal transit time. The study was conducted according to a three-way crossover design with 10 healthy volunteers, each given a non-disintegrating radiolabelled tablet using three different feeding regimens, namely fasted, fed and pre-feed. In the fasted regimen, the tablet was administered after an overnight fast, while in the fed regimen, the tablet was given immediately after a standard breakfast and in pre-feed, the tablet was administered 45 min before the standard breakfast. The time period of 45 min was chosen to maximise the chance of the tablet emptying from the stomach and be present in the proximal small intestine before arrival of food. In accordance with the findings of other studies, the small intestinal transit times of tablets under fasted and fed conditions were not significantly different, with median values of 204 min and 210 min, respectively. However, for pre-feed, there was a significant decrease in the small intestinal transit time (median 100 min) in six volunteers where the tablet has emptied from the stomach before arrival of the meal. In those other four volunteers, the tablet was still in the stomach at 45 min when food was served and the transit behaviour of the tablet was essentially similar to that of the fed state.

The above study provides strong evidence that, intake of food at the time when a dosage form is located in the duodenum can accelerate its passage through the small intestine. The authors explained that this phenomenon is due to increased peristaltic activity of the small intestine in response to the intake of a meal (Kerlin et al., 1982). The increased peristaltic activity helps to clear the small intestine of its luminal contents, thus making room for newly arrived food in the stomach. Schiller et al. (2005) have also reported that, meal can induce a gastro-ileocaecal reflex which initiates the transport of fluids and solids from the distal small intestine into the caecum.

In a study by Digenis et al. (1990), a 50% reduction in bioavailability attributable to more rapid small intestinal transit was observed when enteric coated erythromycin pellets were administered 30 min before food. However, the effect of pre-feed on the small bowel transit time was inconclusive, because erythromycin was reported to possess motilin receptor stimulating activity with a profound effect on gastroduodenal motor activity (Catnach and Fairclough, 1992). On the other hand, Mundy et al. (1989) reported that, no significant difference was observed in the small intestinal transit time of radiolabelled particles administered either fasted or at 1.5 h or 4 h before a meal. The absence of pre-feed effect observed in this study might be related to multiparticulate nature of the dosage form used. Gastric emptying of multiparticulates is more complex and not a single event like in the case of a single unit tablet. Even in the fasted state, the rate and pattern involved in the gastric emptying of multiparticulates/pellets was found to be highly variable (Yuen et al., 1993; Clarke et al., 1995). Thus, the effect of pre-feed is complicated by the proportion of multiparticulates that has emptied into the proximal small intestine at the time when the meal is taken. Certainly more studies need to be conducted to assess pre-feed effects on multiparticulates.

4. Summary

In summary, the transit of pharmaceutical dosage forms in the small intestine takes on average, about 3–4 h and is not influenced by their physical state or the presence of food, albeit the timing of food intake can have an influence. However, there is disagreement among studies regarding the effect of density and size of dosage forms on the small intestinal transit. While, the mean small intestinal transit time is rather consistent among different dosage forms and among studies, individual values can be widely variable. Some excipients can have the potential to modify (increase or decrease) the small intestinal transit time of dosage forms and hence drug bioavailability. More studies are required to examine the influence of excipients on the small intestinal transit of dosage forms and also the effect of food with regard to the timing of intake. Of the methods that have been used to study the small intestinal transit of dosage forms, gamma-scintigraphy can be considered the most reliable and informative, permitting the gastrointestinal transit process to be properly characterised and the transit parameters quantified. However, careful consideration of the interval for image acquisition and proper analysis of the scintigraphic data are important to yield reliable values.

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