International Journal of Pharmaceutics 395 (2010) 2–8

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Gastric emptying of multi-particulate dosage forms

J. Michael Newton

Department of Mechanical Engineering, University College London, Torrington Place, London WC1 7JE, UK

ARTICLE INFO

Article history:
Received 29 April 2010
Accepted 30 April 2010
Available online 19 May 2010

Keywords:
Data processing
Gamma-scintigraphy
Gastric emptying
Gastric motility
Multi-particulate systems

ABSTRACT

The evidence in the literature for the concept that multi-particulate dosage forms below a specific size empty from the stomach as if they were liquids and hence have the potential to provide the best solution to the formulation of controlled release oral dosage forms, has been considered. There is some evidence that particles less than 1.0 mm provide a more rapid response than larger size particles but there is also evidence that this is not always the case and that rapid and reproducible gastric emptying of small particles does not always occur when they are administered. There is strong evidence that food can delay the gastric emptying of multi-particulate systems. Some of the misconception for gastric emptying performance of multi-particulate system is shown to be related to the limitation of the study design and limitation of the way the data is processed. Nevertheless, there is clear evidence that multi-particulate systems can provide effective oral controlled release dosage forms. There is still some way to go with experimental techniques which would allow a definitive answer to the issue of how the variability of the gastric emptying of multi-particulate systems of less than 2.0 mm arises.

Contents

1. Introduction

The constraints of human physiology, biochemical processes and the properties of drug molecules do not allow all drugs to be delivered by the oral route, yet the ability to present a drug via this route provides several advantages to the patient. Of the new drug products registered by the EMEA between 2006 and 2009, 48% were for dosage forms for the oral route as opposed to 45% by injection. The advantages of oral drug administration can be enhanced if the dosage form can be presented in such a way that offers a reduction in the dose frequency or can be used to target a particular section of the gastro-intestinal tract. The methods of providing such dosage forms are described in texts (Vergnaud, 1993; Wise, 2000).

There are 2 basic types, single dose units and multiple dose units, the former usually taking the form of tablets of some type, while the latter are smaller multi-particulate systems of pellets or micro-tablets filled into capsules or compressed into tablets which disintegrate into the original pellets when taken. Of the controlled release products which provide a Summary of Products Characteristics, listed at http://www.medicines.org.uk, the number of single unit dosage systems outnumbers the multi-particulate systems by a considerable margin, in spite of the often quoted advantages which appear for the latter type of product. These advantages can be summarised as follows:

- Easy to coat.
- Can separate incompatible drugs.
- Can mix particles of different drug release rate.
- Reduced risk of dose dumping.
- Reduced risk of local irritation of GI tract.
- Less variable bioavailability.
- Particles <2 mm can pass through the pyloric sphincter even on the feed state and in this respect behave as a liquid in terms of gastric emptying.
- Particles distribute evenly over the GI tract.
- Distribution of particles over the GI tract is generally independent of nutrition status.

E-mail address: m.newton@meng.ucl.ac.uk.

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.04.047

Which of these is used to support the formulation of a multi-particulate system varies with the paper, but association with transit of the pellets in the gastro-intestinal tract is a common feature (Gupta et al., 2001; Ashgar and Chandran, 2006; Hu et al., 2006; Karrout et al., 2009). Judging by the evidence of the greater number of tablet preparations, formulators seem not to believe these claims or there are other factors which influence the decision. When the literature is reviewed to check if there is any support for the superior performance of multi-particulate formulations, there is some support for these claims such as, less intra and inter-subject variability for enteric-coated erythromycin pellets compared to tablets (Graffner et al., 1986; Josefsson et al., 1986). Tada et al. (1989) claimed that pellet formulations were better at producing sustained release effects and reducing variability in blood levels than tablets of theophylline, particularly when administered with food. Based on gamma-scintigraphy evidence, it was claimed that a pellet formulation of metoprolol had shorter gastric emptying times and longer total intestinal residence times than tablets (Abrahamsson et al., 1996). These findings however may not be as clear cut as the authors suggest as they allowed the volunteers to take a second meal before all the preparations had left the stomach. Such a protocol is not ideal, as the second meal can result in the instigation of the 'fed' status in the stomach which will influence the gastric emptying process of any pellets or tablets which are in the stomach when the food is ingested. In contrast to these papers, Dethlefsen et al. (1989) and Schmidt et al. (1989) provided evidence that sustained release tablets of theophylline performed better than pellet preparations. There are, however, a greater number of papers which claim that tablet and pellet preparations are equivalent, usually based on bioavailability studies or clinical performance (Graham, 1979; Upton et al., 1979; Conrad et al., 1982; Newth and Isles, 1982; Duta and Tilley, 1983; Saccar et al., 1983; Edwards et al., 1983; Green et al., 1984; Henneghien et al., 1985; Selen et al., 1985; Tinkelman et al., 1985; Jonkman et al., 1988; Welch et al., 1988; DeBernardi et al., 1997; Marakhovskii et al., 2005). Such findings are not too surprising when most of these papers were often trying to show that a new product was equivalent to an existing product. Where the two types of preparation differed in their performance, there is no certainty that the actual products tested were in fact optimum for the particular systems being tested.

A study which involved the measurement of gastro-intestinal transit by gamma-scintigraphy and plasma levels, claimed to show that a novel pellet formulation (no dimensions provided) of 5-aminosalicylic acid reached the target site of the ileo-caecal region at approximately the same time as the branded tablet formulation used as the standard (Brunner et al., 2003). The lower AUC value for the pellets in comparison to the tablets was suggested to be due to their slower *in vitro* release rate. There could be some issues with these conclusions for gastric transit as the images were taken at 20 or 30 min intervals and there was no indication of how the various gastro-intestinal times for the tablet or pellets were identified. The time values given could have been the first or the last time a tablet or the stated pellet level was seen in a particular region or the mid-time of the observation of the last time seen and the last time not seen at a particular region.

Thus there appears to be no great difference in the performance of multi-particulate and tablet dosage forms. It therefore poses the question as to whether all the claims for benefit of the multi-particulate formulations are valid. Of the several claims listed above, I will restrict my consideration to that associated with gastric emptying.

2. Gastric emptying of pellets

The process of gastric emptying is of fundamental value to ensuring that the supply of nutrients and fluid to the body is maintained. The currently accepted concept in the pharmaceutical literature is set out by Higaki et al. (2008) and reflects the views set out by Camilleri (2006). This involves what has been described as a repeating cyclic pattern (Phases I, II, III and IV) of contractile activity in the stomach, the Migrating Motor Complex (MMC) and the ability to overcome the resistance of the pyloric sphincter. These workers (Higaki et al., 2008) suggest that "in the fed and fasted state, gastric emptying is governed by antral motility in conjunction with pyloric resistance and duodenal feedback mechanism. In the fed state, the MMC is largely abolished: however low amplitude contractions facilitate gastric emptying of small solid particles through the pylorus." They went on to develop a model for the time dependence of oral absorption based on gastric motor activity (Higaki et al., 2008). They included a concept, often reported in the pharmaceutical literature, that there is a limiting size of particles that can empty from the stomach in the fed state and they cited previous studies (Rhie et al., 1998; Choe et al., 2001) based on pharmacokinetics of drug absorption to claim that emptying 0.7 mm particles from the stomach occurred in the fed state, while 3.6 mm particles emptied following the onset of a particular phase (Phase II) of the fasted state. While these studies appear to suggest that pellets of 0.7 mm empty while the stomach is in the fed mode, there were no actual measurements of the position of the pellets in the GI tract, or their emptying from the stomach. Choe et al. (2001) presented data to show that there was no difference in the gastric emptying of the two sizes of pellets in the fasted state but significant differences in the $t_{initial}$ when the volunteers took the pellets with either a small liquid meal or standard meal. A previous study (Damle et al., 2001) found that on average didanosine formulated either as enteric-coated pellets (diameter 2 mm) or enteric-coated tablets (5 mm in diameter) indicated that the drug was absorbed faster from the beads than the tablets when administered to fasted volunteers. In contrast with Choe et al. (2001) and Rhie et al. (1998) however, they found that tablets emptied faster, 0.17–1.67 h (mean 0.55 h) than the beads, 0.33–3.33 h (mean 0.81 h). The studies use the pharmacokinetic results to support their findings and average values of the parameters considered (Rhie et al., 1998; Choe et al., 2001; Higaki et al., 2008). This does not mean that the effects they report occur in every individual on every occasion.

There are numerous gamma-scintigraphy studies which show that, the presence of food delays gastric emptying, usually judged by t_{50} values of pellets of the usual size range (0.7–1.4 mm) (Hunter et al., 1982; Davis et al., 1986a,b, 1987; Kaniwa et al., 1988; Devereux et al., 1990; Digenis et al., 1990; Wilding et al., 1991, 1992a; Coupe et al., 1993; Yuen et al., 1993; Kenyon et al., 1995; Meyer and Lake, 1997; Meyer et al., 2001). This delay was also demonstrated for pellets as small as 0.10–0.5 mm (Beten et al., 1996) and as large as 3 mm (Blok et al., 1991). If the results for the time before any pellets empty from the stomach (the lag time) are considered, there was no significant difference whether the pellets were administered in the fasted or fed state (Devereux et al., 1990) nor was there any significant difference in the lag times between 0.5 and 4.75 mm pellets administered in the fasted state (Clarke et al., 1993). In contrast to these results, it was found that, administration of pellets after food resulted in lag time for gastric emptying of pellets being longer than those administered under fasted conditions (Kaniwa et al., 1988). This extension of the lag time for dosing pellets in the fed state was also observed by Yuen et al. (1993) but not for all volunteers.

The gastric emptying of pellets from the stomach has been found to be longer in fed than fasted volunteers, but these results may have been influenced by the fact that, due to the prolonged delay in completion of gastric emptying in some of the fed volunteers, the volunteers received a second meal before all the pellets emptied from the stomach (Devereux, 1987). This resulted in the onset of fed state, which in several cases extended times for the emptying

of the pellets. We had an extreme example of this in an unreported study, where because the protocol was set up to evaluate the blood levels of a drug in addition to gastric transit of the pellets, a standardised feeding routine of 4 h after administration of the dosage form was used. In this study for 2 of the 6 volunteers, no pellets (1.0–1.4 mm diameter) had emptied from the stomach at 4 h and even with a further meal, at 8 h, such that these individuals still had 100% of pellets in the stomach at the end of the 12 h of the study. It is difficult to accommodate this data into the usual average system, but omitting these 2 volunteers from the results put a different perspective on the conclusion. Thus the concept that pellets less than 2 mm can empty from the feed stomach, did not apply in these cases. Coupe et al. (1993) also noted variations in the behaviour of volunteers in terms of when pellets emptied in association with the emptying of food.

In a study of pancreatin preparations available on the market (Pancrease, pellet diameter 2.0 mm, and Creon 20, pellet diameter about 1.18 mm diameter), it was noted that, gastric emptying of radio-labelled model pellets of equivalent diameter taken in association with the two preparations, determined by gamma-scintigraphy, indicated that there was no significant difference in the emptying parameters determined by fitting an exponential function to the data between the two pellet diameters (Meyer and Lake, 1997). The use of the curve fitting system can be questioned as gastric emptying of pellets is rarely exponential, as can the fact that some of the individual results provided t_{50} values considerably in excess of the time used to monitor the gastric emptying (e.g. 526, 634 and 872 min, compared to monitoring time of 300 min). They had reported the same equivalent gastric emptying behaviour for these two preparations in a previous study, based on gamma-scintigraphy but using the $\sqrt{}$area under the % pellets in the stomach as a function of time as a quantification of the gastric emptying process (Meyer et al., 2001). Both these studies involved administration of a lipid component as a component of the feeding conditions. The percentage of pellets leaving the stomach in the first 150 min was significantly lower (paired *t*-test) than the percentage of radio-labelled oil. The similarity in the gastric emptying of these two preparations goes some way towards the observation that they performed with similar effectiveness in the clinical situation (Duta and Tilley, 1983; Beverley et al., 1987; Williams et al., 1990; Bruno et al., 1998). Hillel et al. (1998) incorporated resin beads of diameter 0.3–1.18 mm into capsules containing the 2 mm Creon pellets to compare them with the radio-labelled food to the gastric emptying behaviour. In 4 out of 5 cystic fibrosis patients, the pellets had t_{50} emptying values less than the food, whereas the remaining patient had a t_{50} value greater for the pellets than the food. A higher mean value of t_{50} for radio-labelled pellets (2.00 diameter) mixed with 2.0 mm pancreatin pellets than radio-labelled food was observed in healthy volunteers (Halm et al., 1999). It is difficult to say whether it was the food or the pellets that had the higher t_{50} values in the case of the subjects with pancreatitis in this paper as there is an uncertainly in the t_{50} values in Tables 1 and 2 of their paper, although the graphs (Fig. 1 in their paper) for the gastric emptying process do show that the pellets tend to empty faster than the food in the subjects with pancreatitis. The values for the $^{14}CO_2$ breath test to measure the enzyme function, do show that on average the release is faster in the case of the volunteers than the patients, which tends to indicate that pellet transit is faster in the healthy volunteers than the patients, in spite of their reported slower gastric emptying (Hillel et al., 1998). The clinical significance of administration of pancreatin pellets <1.25 mm as opposed to the standard formulation of pellets >1.25 mm failed to identify any significant effect (Halm et al., 1999).

The simple concept of there being a cut off dimension of 2.0 mm which is based on studies with fistulised dogs (Meyer et al., 1979, 1985) as pointed out by Coupe et al. (1993), may not give the full picture. There is a need to identify with greater certainty the relative effects of the movement of materials in the stomach and the situation at the pyloric sphincter. Studies involving monitoring gastric motility such as those by Coupe et al. (1991), Rhie et al. (1998), Higaki et al. (2008) and Goodman et al. (2010) will provide some assistance with the understanding of what is happening. Gastric motility studies however, are not without their problems. They are invasive and can cause disturbance of the gastro-intestinal motility they are trying to measure. Both Rhie et al. (1998) and Higaki et al. (2008) also used pharmacokinetics parameters as opposed to direct observation to identify gastric emptying of the dosage form, the latter paper used viscous calorific liquid feeds as opposed to solid meals and seems only to have monitored motility for 4 h. Values in excess of 4 h have been observed for the complete emptying of pellets from the stomach, even in the fasted state (Devereux, 1987; Clarke et al., 1993, 1995). Coupe et al. (1993) attempted to answer the question as to whether pellets emptied from the stomach with food, by administration of radio-labelled pellets (0.8–1.1 mm diameter) and the food and followed emptying by gamma-scintigraphy, while monitoring gastric motility with a pressure sensitive device which allowed remote collection of data. They found that in 2 of the 8 subjects pellets and food emptied at similar rates, whereas in 6 of the subjects the pellets emptied from the stomach at a slower rate. When the gastric emptying of 3 and 10 mm tablets were monitored in association with a solid meal, Podczeck et al. (2007) found that the tablets invariably emptied after the food had left the stomach. In a study of the influence of feeding conditions on the gastric emptying of a10 mm diameter tablet and food determined by gamma-scintigraphy, where gastro-intestinal motility was also monitored for at least 6 h, Mitchell (1997) found that identification of the phases of gastric motility was subjective. The indications were that the emptying of the10 mm tablets occurred in a different phase of the motility cycle, depending on what was co-administered with the tablet, a simple 5% dextrose solution, a nutrient drink or a solid meal. The most consistent was the simple dextrose solution, with 7 out of 10 subjects tablet emptying occurring in Fed/Phase II, 2 in Phases I and 1 in Fed/Phase II. For feeding with beef extract, the tablets emptied in Phase I (1), Phase II (3), Phase II/III (1), Phase II/Fed (3) and Fed (2). For feeding with the solid meal (Shepherd's pie) each of 4 subjects emptied the tablets in fed and Fed/Phase II, while the remaining two subjects emptied the tablets in either Phase I or II. There is clearly more work to be done to relate gastric motility to emptying of dosage forms.

Table 1
Gastric emptying results based on simulated emptying profiles presented in Fig. 1. The "exact" values are taken from the simulations (see Fig. 1), whereas the "estimates" are calculated on the basis of different time intervals between measurements. t_{50} = time for 50% of pellets to have emptied from the stomach, lag time = time for 10% of pellets to have emptied from the stomach, n.d. an estimate cannot be calculated.

Measuring interval	Volunteer 1	Volunteer 2	Volunteer 3
t_{50} values			
Exact value	13 min	34 min	35 min
5 min	13 min	34 min	35 min
10 min	15 min	34 min	32 min
15 min	10 min	35 min	32 min
20 min	12 min	33 min	26 min
25 min	14 min	37 min	29 min
30 min	16 min	37 min	34 min
Lag times			
Exact value	10 min	23 min	15 min
5 min	10 min	20 min	15 min
10 min	10 min	20 min	10 min
15 min	n.d.	15 min	15 min
20 min	n.d.	n.d.	n.d.
25 min	n.d.	n.d.	n.d.
30 min	n.d.	n.d.	n.d.

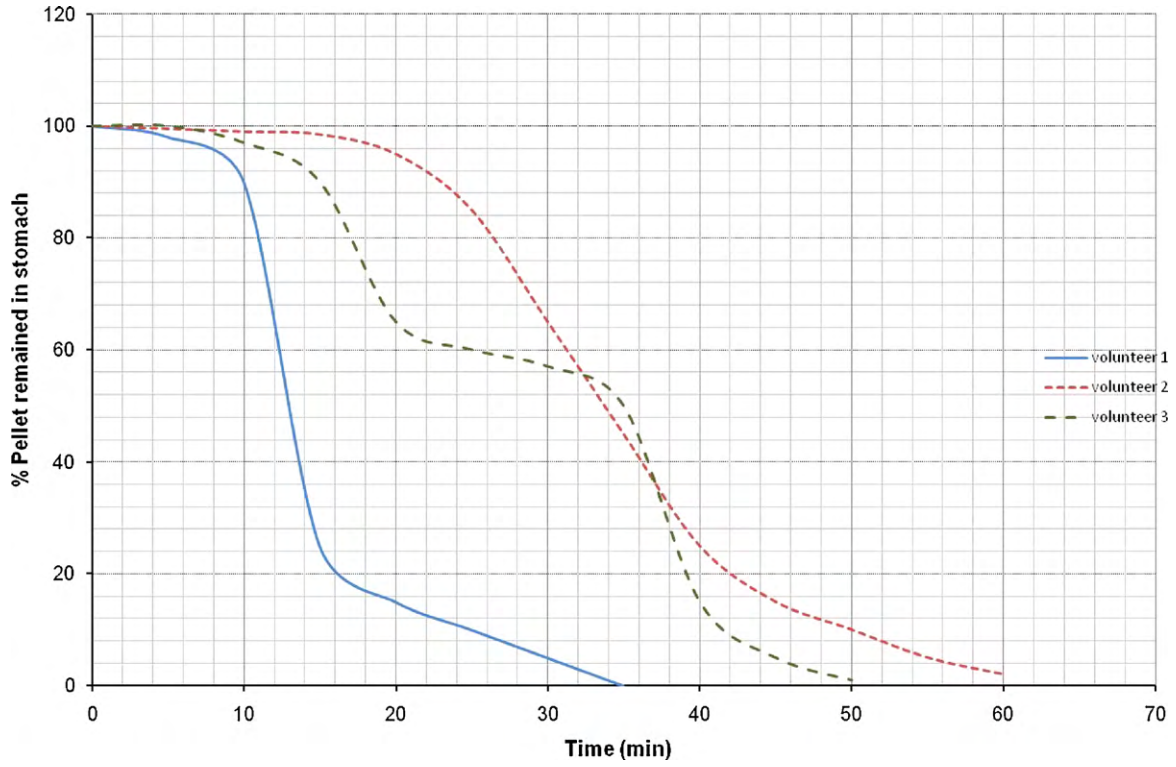

Fig. 1. Simulated pellet gastric emptying data for parameter determination as listed in Table 1.

3. Problems of the assessment of the literature values for gastric emptying of pellets taken from gamma-scintigraphy

Many of the publications reporting gastric emptying studies quote gamma-scintigraphy as being the "gold standard" approach. It must however always be remembered that it does not identify anatomical features, has limitations of resolution and is sensitive to how the observations are made. As early as 1982 it was noted that the position of the volunteer, whether upright or supine was important (Hunter et al., 1982).

Rather than reviewing in detail individual papers, I should like to point out some general issues with the interpretation of the reported data from gamma-scintigraphy studies. The basic system involves observing the body through a collimator, which focuses any emitted gamma rays onto a large scintillation crystal of thallium activated sodium iodide, which is coupled by light guides to an array of photomultiplier tubes. The output from these tubes is connected to image forming electronics and it is these that are observed. It is possible to use a source of different energy levels thus allowing simultaneous monitoring of different dosage forms and/or food. Spatial resolution of the source of the gamma rays falls away as its distance from the collimator increases. Also body tissues attenuate the transited energy levels, and a different result will be obtained if an anterior or posterior image is taken. To avoid the problem of delay in taking first one image then the other, double headed cameras are sometimes used in the studies (Devereux, 1987; Devereux et al., 1990; Clarke et al., 1993, 1995; Yuen et al., 1993; Mitchell, 1997; Podczeck et al., 2007). The time taken to acquire an image depends on the activity of the source, the higher the level, the shorter the time. Typical times vary between 30 s and 5 min. The likelihood of the source changing its position during imaging increases with the length of time required to obtain an appropriate count level. To reduce the possible adverse effects on the subjects, levels of radio-activity used are usually restricted to a level that is acceptable to the appropriate committee. Thus the time taken to obtain the image and the time between images are an important factor in the determination of gastric emptying, the longer the time between measurements, the less accurate are the results. This is also illustrated using the simulation shown in Fig. 1 where theoretical gastric emptying curves are presented. The estimates for the time for 50% of the pellets to empty from the stomach (t_{50}) for different observation intervals are given in Table 1. As can be seen for volunteer 3, t_{50} values are in fact meaningless due to the biphasic emptying curve i.e. whether and which curve parameters to use is another issue in data evaluation and will be discussed later. The need for frequent measuring intervals becomes even more obvious when comparing the lag times i.e. the time spans until 10% of pellets have been emptied from the stomach. These can only be determined accurately with 5 or maximal 10 min measurement intervals. Clearly it is difficult to compare studies that use different times of observation.

Another advantage of making frequent observations is associated with the identification of the position of the pellets within the subject. The stomach is not a static organ in terms of position and size. To identify the proportion of pellets that remain in the stomach, the usual procedure is to identify a "region of interest", and obtain the count value as a % of the original count. This can be quite subjective. Drawing this region is critical, too small and the pellets could be considered out of the stomach when they are in fact still there, too large and the pellets could be counted as in the stomach when in fact they have left. The movement involved with emptying can be quite small, and taking frequent measurements does help with the identification of the position of the pellets within the GI tract.

As noted by McConnell et al. (2008), the approach of Davis et al. (1986a,b) using a meta-analysis of the literature values for gastric transit data results in "mean values from pooled data with different methodologies and is often taken out of context." They compared the values for small intestinal transit time of non-disintegrating pellets of 1–1.4 mm diameter in 1 individual on 8 occasions (McConnell et al., 2008). They demonstrated that the average range quoted by the meta-analysis was obtained, but that

this value only occurred in 2 of the 8 occasions. A similar approach for the gastric emptying taken from the results of Devereux (1987) and Clarke (1989), and the mean values and range of values in minutes of the lag time before pellets started to empty t_L, the time for 50% to empty from the stomach t_{50} and the time for the pellets to completely empty from the stomach t_{comp} was determined. The values for pellets of 1.0–1.4 mm in diameter, taken under fasted conditions by the same volunteer on seven different occasions are: t_L 71.6 (40–71.6), t_{50} 122.9 (64–185) and t_{comp} 168.6 (88–220) min. Clearly there is considerable variation in the same individual on the different occasions in spite of attempts to standardise the conditions associated with the observations and such an observation is a common feature of many of the publications. In an unreported study comparing two coatings of pellets under fasted conditions, we had 1 volunteer who emptied from the stomach what must have been the complete capsule containing pellets by 3 min, while in the second arm of the study, there was a lag time of 180 min before emptying started.

Another problem associated with the use of average values was pointed out by Podczeck and Newton (1996). The average curve for the % of pellets remaining in the stomach with time are reported by several authors (e.g. Davis et al., 1984, 1987; O'Reilly et al., 1987; Wilson et al., 1989; Caner et al., 1991; Wilding et al., 1992a,b; Meyer et al., 2001) as opposed to curves for a given individual (e.g. Hunter et al., 1982; Jenkins et al., 1983; Blok et al., 1991; Clarke et al., 1993, 1995; Coupe et al., 1993; Yuen et al., 1993). Kenyon et al. (1995) fitted an exponential function to the graphs, for average gastric emptying curves, yet not one of the individual sets of the results followed such a curve as was noted by Podczeck and Newton (1996). The use of average curves can clearly lead to misinterpretation of the nature of the gastric emptying process. Coupe et al. (1993) had in fact warned of the potential dangers of using average curves but this appears to have gone unheeded in many instances, even by members of the same group of workers. An extreme example is provided where average curves, with only 3 time intervals do not reflect the true situation for the gastric emptying of pellets (Wilson et al., 1998). The use of an exponential function to model the gastric emptying of pellets also provides a limitation to the model used by Watanalumlerd et al. (2007). In their approach to model the pharmacokinetics and simulation of transit effects of mixed immediate release and enteric-coated pellet formulations. Similar limitations in the use of pharmacokinetics also apply to those papers which rely solely on this type of analysis to arrive at times for gastric emptying e.g. Peh and Yuen (1996), Rahman et al. (2005). The values provided are only an approximation of what is actually taking place.

Coupled with the use of curves for each volunteer, Podczeck et al. (1995) demonstrated that, a better approach which allowed the use of the whole of the curve representing the % of pellets remaining as a function of time was to use statistical moments to calculate the Mean Gastric Residence Time (MGRT) and the Variance of the Gastric Residence Time (VGRT). Such an approach allows for the considerable variation in the shape of the gastric emptying curves, which often appears associated with clusters of pellets moving rather than a constant stream. This fits the concepts of the presence of intermittent contractile pulses known to occur in the stomach (Borley, 2005).

There are also issues with defining the gastric emptying curves. As pointed out with the clinical use of gamma-scintigraphy, there are issues of cost associated with such studies (Abell et al., 2008). There are also problems of maintaining the volunteer in a constant position over prolonged periods of times. Therefore many studies employ considerable intervals between observations to allow several volunteers to participate in the study on one day as opposed to continuous monitoring of an individual volunteer. While external markers on the volunteers are used to identify the position of the volunteer in association with the gamma-camera, repositioning is not the only issue. The position and the dimensions of the stomach are known to change with time (Borley, 2005). By monitoring regularly, it is possible to ensure a more reproducible assessment of when material exits the stomach. There is certainly some tedium involved for the volunteer with frequent monitoring, but the rewards in terms of the quality of the results in understanding they provide, are well worth the effort.

4. The current situation

There is clearly more work to be done to support the claim that pellet formulations will always function better than single unit dosage forms in terms of gastro-intestinal transit. The simplistic claim that there is a limiting dimension of 2 mm which always allows gastric emptying of pellets with food, and that pellets smaller than this empty in a first order process as if they were a liquid, often quoted, cannot be justified by the existing literature. The reasons for this are associated with the physiological process of gastric emptying and the classical description reported in much of the pharmaceutical literature does not fully explain what is actually happening. A better understanding should come from the mathematical modelling of Pal et al. (2004), coupled with MRI studies reported by Pal et al. (2007). In this work the internal structure and the changes in dimension occurring in the stomach are considered, not just the pressure changes monitored in motility studies. Higaki et al. (2008) claimed that the concept of the "Magenstrasse" was not helpful in explaining the absence of significant levels of drug plasma levels. However, I think that this approach is still the best way forward to date. Limited assistance will come from general clinically studies of the process which are usually concerned with the identification of changes in gastric emptying or motility in patients and the best use of resources. The "Consensus recommendations for gastric emptying Scintigraphy", a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine (Abell et al., 2008) describes procedures that have been accepted for this function. The procedures described would not however be of much value in the evaluation of the gastric emptying of dosage forms. The selection of only 4 time points is included "to alleviate some of the concerns at some imaging centres that GES is too time consuming, and the efficiencies in camera use are associated with little loss of test accuracy." (Abell et al., 2008), but would be totally inadequate to identify what was happening to dosage forms. The need to monitor the movement of differing segments of the stomach, the dimensions of the pyloric sphincter, the position of the dosage form and the food in the stomach, the motility status of the gastro-intestinal tract, coupled with the measurement of the absorption of the drug, provides a complex study. While such a study could provide knowledge what is actually happening, it might not add much to improving the treatment of the patient. At the moment both well formulated multi-unit and single-unit systems appear to offer an approach to providing controlled release oral dosage forms.

5. Conclusions

The issue of how pellets empty from the stomach is not as well defined as the secondary pharmaceutical literature suggests. Claims that pellets smaller than 2 mm will empty from the stomach as if they were liquids in the fed state cannot be supported by the literature. Closer examination of the experiments used to provide these claims shows that there can be flaws in the design of the study protocol and/or analysis of the data. There is need to identify in greater detail, with improved monitoring techniques, just what is happening before a final explanation of the reasons for the considerable variation of the way multi-particulates empty from the

stomach under fasted and fed conditions can be answered. There is, however, clear evidence that pellet formulations can be used to provide effective controlled release oral formulations.

References

Abell, T.L., Camilleri, M., Donohoe, K., Hasler, W.L., Lin, H.C., Maurer, A.H., McCallum, R.W., Nowak, T., Nusynowitz, M.L., Parkman, H.P., Shreve, P., Szarka, L.A., Snape Jr., W.I., Ziessman, H.A., 2008. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. Am. J. Gastroenterol. 103, 753–763.

Abrahamsson, B., Alpsten, M., Jonsson, U.E., Lundberg, P.J., Sandberg, A., Sundgren, M., Svenheden, A., Tölli, J., 1996. Gastro-intestinal transit of a multi-unit formulation (metoprolol CR/ZOK) and a non-disintegrating tablet with the emphasis on colon. Int. J. Pharm. 140, 229–235.

Ashgar, L.F., Chandran, S., 2006. Multiparticulate formulation approach to colon specific drug delivery: current perspectives. J. Pharm. Pharm. Sci. 9, 327–338.

Beten, D.B., Van Gansbeke, B., Schoutens, A., Moës, A.J., 1996. Evaluation of the gastric behaviour of co-evaporate particles under fasting and non-fasting conditions. Int. Pharm. 123, 145–147.

Beverley, D.W., Kelleher, J., MacDonald, A., Littlewood, J.M., Robinson, T., Walters, M.P., 1987. Comparison of four pancreatin extracts in cystic fibrosis. Arch. Dis. Childhood 62, 564–568.

Blok, D., Arndt, J.W., de Haan, F.H.N., Vermeij, P., Junginger, H.E., Pauwels, E.K.J., 1991. Scintigraphic investigation of the gastric emptying of 3 mm pellets in human volunteers. Int. J. Pharm. 73, 171–176.

Borley, N.R., 2005. Gastrointestinal tract, stomach and abdominal oesophagus. In: Standing, S. (Ed.), Gray's Anatomy. The Anatomical Basis of Clinical Practice, 39th edition. Elsevier, London, pp. 1143–1152 (Chapter 71).

Brunner, M., Greinwald, B., Kletter, K., Kvaternik, H., Corrado, M.E., Eichler, H.G., Müller, M., 2003. Gastrointestinal transit and release of 5-aminosalicylic acid from ^{153}Sm-labelled mesalazine pellets vs. tablets in male healthy volunteers. Aliment. Pharmacol. Therap. 17, 1163–1169.

Bruno, M.J., Borm, J.J.J., Hoek, F.J., Delzenne, B., Hofmann, A.F., de Goeij, J.J.M., van Royen, E.A., van Leeuwen, D.J., Tytgat, G.N.J., 1998. Gastric transit and pharmacodynamics of a two-millimeter enteric-coated pancreatin microsphere preparation in patients with chronic pancreatitis. Digest. Dis. Sci. 43, 203–213.

Camilleri, M., 2006. Integrated upper gastrointestinal response to food intake. Gastroenterology 131, 640–658.

Caner, B.E., Ercan, M.T., Kapucu, L.O., Tuncel, S.A., Bekdik, C.F., Erbengi, G.F., Piskin, E., 1991. Functional assessment of human gastrointestinal tract using ^{99}Tc^{m}-latex particles. Nucl. Med. Commun. 12, 539–544.

Choe, S.Y., Neudeck, B.L., Welage, L.S., Amidon, G.E., Barnett, J.L., Amidon, G.L., 2001. Novel method to assess gastric emptying in humans: pellet gastric emptying test. Eur. J. Pharm. Sci. 14, 347–353.

Clarke, G.M., 1989. Gastrointestinal transit of spherical granules of differing size and density. Ph.D. Thesis, University of London.

Clarke, G.M., Newton, J.M., Short, M.D., 1993. Gastrointestinal transit of pellets of differing size and density. Int. J. Pharm. 100, 81–92.

Clarke, G.M., Newton, J.M., Short, M.D., 1995. Comparative gastrointestinal transit of pellet systems of varying density. Int. J. Pharm. 114, 1–11.

Conrad, G.J., Jernberg, M.J., Wong, F.N., Mildon, C.A., French, I.W., 1982. Clinical assessment of theophylline absorption from Theolair-SR and two other sustained release formulations relative to a conventional formulation. Int. J. Pharm. 10, 259–273.

Coupe, A.J., Davis, S.S., Evans, D.F., Wilding, I.R., 1991. Correlation of the gastric emptying of non-disintegrating tablets with gastrointestinal mobility. Pharm. Res. 10, 1281–1285.

Coupe, A.J., Davis, S.S., Evans, D.F., Wilding, I.R., 1993. Do pellet formulations empty from the stomach with food? Int. J. Pharm. 92, 167–175.

Damle, B., Ullah, I., Doll, W., Wiley, G., Knupp, C., 2001. Pharmacokinetics and gamma-scintigraphy evaluation of two enteric coated formulations of didanosine in healthy volunteers. Br. J. Clin. Pharmacol. 54, 255–261.

Davis, S.S., Hardy, J.G., Fara, J.W., 1986a. Transit of pharmaceutical dosage forms through the small intestine. Gut 27, 886–892.

Davis, S.S., Khosla, R., Wilson, C.G., Washington, N., 1987. Gastrointestinal transit of controlled-release pellet formulation of tiaprofenic acid and the effect of food. Int. J. Pharm. 35, 253–258.

Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R., Wilson, C.G., 1984. The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). Int. J. Pharm. 21, 331–340.

Davis, S.S., Stockwell, A.F., Taylor, M.J., Hardy, J.G., Whalley, D.R., Wilson, C.G., Bechgaard, H., Christensen, F.N., 1986b. The effect of density on the gastric emptying of single and multiple unit dosage forms. Pharm. Res. 3, 208–213.

DeBernardi, M., DeBernardi, F., Colombo, P., 1997. Randomized crossover comparison of the pharmacokinetic profiles of two sustained release morphine sulphate formulations in patients with cancer related pain. Clin. Drug Invest. 14, 28–33.

Dethlefsen, U., Repges, R., Werdermann, K., 1989. Theophylline-Retardformulierungen im Vergleich. Atemwegs- und Lungenkrankheiten 15, 367–372.

Devereux, J.E., 1987. Gastrointestinal transit of multiple unit dosage forms. Ph.D. Thesis, University of London.

Devereux, J.E., Newton, J.M., Short, M.B., 1990. The influence of density on the gastrointestinal transit of pellets. J. Pharm. Pharmacol. 42, 500–501.

Digenis, G.A., Sundefer, E.P., Parr, A.F., Beihn, R., McClain, C., Scheinthal, B.M., Ghebre-Sellassie, I., Iyer, U., Nesbitt, R.U., Randinitis, E., 1990. Gastrointestinal behaviour of orally administered radio-labelled erythromycin pellets in man as determined by gamma scintigraphy. J. Clin. Pharmacol. 30, 621–631.

Duta, S.K., Tilley, D.K., 1983. The pH-sensitive enteric- coated pancreatic enzyme preparations: an evaluation of therapeutic efficacy in adult patients with pancreatic insufficiency. J. Clin. Gastroenterol. 5, 51–54.

Edwards, C., Cope, A.S., Jackson, A.H., Purkiss, R., 1983. The comparative bioavailability of slow release oral theophylline preparations. J. Clin. Hosp. Pharm. 8, 63–67.

Goodman, K., Hodges, L.A., Band, J., Stevens, H.N.E., Weitschies, W., Wilson, C.G., 2010. Assessing gastrointestinal motility and disintegration profiles of magnetic tablets by a novel magnetic imaging device and gamma scintigraphy. Eur. J. Pharm. Biopharm. 74, 84–92.

Graffner, C., Josefsson, K., Stockman, O., 1986. Intra- and inter-subject variation of erythromycin absorption from single-unit and multi-unit enteric coated products. Biopharm. Drug Dispos. 7, 163–171.

Graham, D.Y., 1979. An enteric-coated pancreatic enzyme preparation that works. Digest. Dis. Sci. 24, 906–909.

Green, L.D., Saccar, C.L., Helsel, C.L., Niehls, M.E., McGeady, S.J., Mansmann Jr., H.C., 1984. Forty-eight hour absorption pharmacokinetic profiles of two sustained release theophylline preparations. J. Asthma 21, 35–39.

Gupta, V.K., Beckert, T.E., Price, J.C., 2001. A novel pH time delivery multi-unit potential colonic drug delivery system. I. Development. Int. J. Pharm. 213, 83–91.

Halm, U., Löser, C., Löhr, M., Katschinski, M., Mössner, J., 1999. A double-blind, randomized, multicentre, crossover study to prove equivalence of pancreatin mini-microspheres versus microspheres in exocrine pancreatic insufficiency. Aliment. Pharmacol. Therap. 13, 951–957.

Henneghien, C., Remacle, P., Bruart, J., Jonckheer, J., 1985. A double blind crossover study of the steady state plasma pharmacokinetics of two sustained-release theophylline preparations. Acta Therap. 11, 363–373.

Higaki, K., Choe, S.Y., Löbenberg, R., Welage, L.S., Amidon, G.L., 2008. Mechanistic understanding of time-dependent oral absorption based on gastric motor activity in humans. Eur. J. Pharm. Biopharm. 70, 313–325.

Hillel, P.G., Tindale, W.B., Taylor, C.J., Frier, M., Senior, S., Ghoshal, S., 1998. The use of dual-isotope to compare the gastrointestinal transit of food and pancreatic enzyme pellets in cystic fibrosis patients. Nucl. Med. Commun. 19, 761–769.

Hu, L.-D., Lui, Y., Tang, X., Zhang, Q., 2006. Preparation and in vitro/in vivo evaluation of sustained-release metformin hydrochloride pellets. Eur. J. Pharm. Biopharm. 64, 185–192.

Hunter, E., Fell, J.T., Sharma, H., 1982. The gastric emptying of pellets contained in hard gelatin capsules. Drug Develop. Ind. Pharm. 8, 751–757.

Jenkins, J.R.F., Hardy, J.G., Wilson, C.G., 1983. Monitoring antacid preparations in the stomach using gamma scintigraphy. Int. J. Pharm. 14, 143–148.

Jonkman, J.H.G., Steinijans, V.W., Beier, W., Yska, J.P., Kerkhof, F.A., de Noord, O.E., Grasmeyer, G., 1988. Sustained release properties of the once daily theophylline capsule Euphylong as compared with Theo-Dur tablets. Int. J. Pharm. 43, 139–143.

Josefsson, K., Levitt, M.J., Kann, J., Bonn, C., 1986. Erythromycin absorption from enteric-coated pellets given in multiple doses to volunteers in comparison with enteric-coated tablets and film coated tablets. Curr. Therap. Res. Clin. Exp. 39, 131–142.

Kaniwa, N., Aoyagi, N., Ogata, H., Ejima, A., Motoyama, H., Yasumi, H., 1988. Gastric emptying rates of drug preparations. II. Effects of size and density of enteric-coated drug preparations and foods on gastric emptying rates in humans. J. Pharmacobio-Dynam. 11, 571–575.

Karrout, Y., Neut, C., Wils, D., Siepmann, F., Deremaux, L., Flament, M.-P., Dubreuil, L., Desreumaux, P., Siepmann, J., 2009. Novel polymeric film coating for colon targeting: drug release from coated pellets. Eur. J. Pharm. Sci. 27, 427–433.

Kenyon, C.J., Hooper, G., Tierney, D., Butler, J., Devane, J., Wilding, I.R., 1995. The effect of food on the gastrointestinal transit and systemic absorption of naproxen from a novel sustained release formulation. J. Control. Rel. 34, 31–36.

Marakhovskii, Y.K., Fixa, B., Holomán, J., Hulek, P., Bátovský, M., Hildebrand, T., Rumyantsev, V.G., Grigoryeva, G., Stolte, M., Vieth, M., Greinwald, R., The International Salofalk Study Group, 2005. Dose-escalation improves 5-ASA response in active ulcerative colitis. Results from a clinical trial comparing novel mesalazine pellets with mesalazine tablets. Aliment. Pharmacol. Therap. 21, 133–140.

McConnell, E.L., Fadda, H., Basit, A.W., 2008. Gut instincts: explorations in intestinal physiology and drug delivery. Int. J. Pharm. 364, 213–226.

Meyer, J.H., Lake, R., 1997. Mismatch of duodenal deliveries of dietary fat and lipase from enterically coated microspheres of pancreatin. Pancreas 15, 226–235.

Meyer, J.H., Lake, R., Elashoff, J.D., 2001. Postcibal gastric emptying of pancreatin pellets. Effect of dose and meal oil. Digest. Dis. Sci. 46, 1846–1852.

Meyer, J.H., Dressman, J., Fink, A., Amidon, G., 1985. Effect of size and density on canine gastric emptying of non-digestible solids. Gastroenterology 89, 805–813.

Meyer, J.H., Thomson, J.B., Cohen, M.B., Shadchehr, A., Mandiola, S.A., 1979. Sieving of solid food by the canine stomach and sieving after gastric surgery. Gastroenterology 76, 804–813.

Mitchell, C.L., 1997. The relationship between motility and gastrointestinal transit of tablets. Ph.D. Thesis, University of London.

Newth, C.J.L., Isles, A.F., 1982. Comparison at steady state of sustained-release theophylline tablets and capsules. J. Asthma 19, 145–149.

O'Reilly, S.G., Wilson, C.G., Hardy, J.G., 1987. The influence of food on the gastric emptying of multi-particulate dosage forms. Int. J. Pharm. 34, 213–218.

Pal, A., Brasseur, J.G., Abrahamsson, B., 2007. A stomach road or "Magenstrasse" for gastric emptying. J. Biomech. 40, 1202–1210.

Pal, A., Indireshkumar, K., Schwizer, W., Abrahamsson, B., Fried, M., Brasseur, J.G., 2004. Gastric flow and mixing studies using computer simulation. Proc. Roy. Soc. Lond. B 271, 2587–2594.

Peh, K.K., Yuen, K.H., 1996. Indirect gastrointestinal transit monitoring and absorption of theophylline. Int. J. Pharm. 139, 95–103.

Podczeck, F., Newton, J.M., 1996. Letter to editor. J. Control. Rel. 41, 291–293.

Podczeck, F., Newton, J.M., Yuen, K.H., 1995. The description of the gastrointestinal transit of pellets assessed by gamma scintigraphy using statistical moments. Pharm. Res. 12, 376–379.

Podczeck, F., Mitchell, C.L., Newton, J.M., Evans, D., Short, M.B., 2007. The gastric emptying of food as measured by gamma-scintigraphy and electrical impedance tomography (EIT) and its influence on the gastric emptying of tablets of different dimensions. J. Pharm. Pharmacol. 59, 1527–1538.

Rahman, N.-R., Yuen, K.H., Woel, W.J., 2005. Gastrointestinal transit monitoring and absorption of controlled-release pellets of diltiazem. Pharm. Develop. Technol. 10, 371–379.

Rhie, J.K., Hayashi, Y., Welage, L.S., Frens, J., Wald, R.J., Barnett, J.L., Amidon, G.E., Putcha, L., Amidon, G.L., 1998. Drug marker absorption in relation pellet size, gastric motility and viscous meals in humans. Pharm. Res. 15, 233–238.

Saccar, C.L., Green, L.D., Helsel, C.L., Niehls, M.E., Diconcetto, J.A., Mansmann Jr., H.C., McGeady, S.J., 1983. Pharmacokinetic characteristics of a new sustained release theophylline capsule with longer absorption profiles: single and multiple dosing bioavailability studies. Ann. Allergy 50, 245–248.

Schmidt, M., Pfeifer, M., Heinrich, J., 1989. Slow release theophylline capsules vs tablet: serum levels and lung function. Atemwegs und Lungenkrankheiten 15, 567–572.

Selen, A., Johnson, C.A., Rogge, M.C., Craig, W.A., Welling, P., 1985. Absorption of theophylline from two sustained release formulations. Biopharm. Drug Dispos. 6, 217–221.

Tada, H., Ishikawa, M., Sato, E., Suzuki, T., Unno, K., Miura, K., Ohmiya, Y., Nakait, K., 1989. Influence of food on bioavailability from two controlled-release granules of theophylline. J. Clin. Pharm. Therap. 14, 145–151.

Tinkelman, D.G., Miller, E., Janky, D.G., Decouto, J., Edelman, L., 1985. A comparative trial of the clinical efficacy and pharmacokinetics of 12-hour and 24-hour controlled release theophylline preparations in patients with chronic asthma. Ann. Allergy 55, 571–576.

Upton, R.A., Thiercelin, J.-F., Guentert, T.W., Sansom, L., Powell, J.R., Coates, P.E., Riegelman, S., 1979. Evaluation of the absorption from some commercial sustained-release products. J. Pharm. Biopharm. 8, 131–149.

Vergnaud, J.M., 1993. Controlled Release of Oral Dosage Forms. Ellis Horwood Ltd., Chichester, UK.

Watanalumlerd, P., Mark, C.J., Ayres, J.W., 2007. Pharmacokinetic modeling and simulation of gastrointestinal transit of plasma concentrations of drugs from mixed immediate-release and enteric-coated pellet formulations. Pharm. Develop. Technol. 12, 193–202.

Welch, M.J., Orgel, H.A., Meltzer, E.O., Kemp, J.P., Tinkelman, D.G., 1988. Comparison of a new sustained-release theophylline preparation, Theo-beads, with Theo-Dur tablets in children with asthma. J. Asthma 25, 269–274.

Wilding, I.R, Hardy, J.G., Maccari, M., Ravelli, V., Davis, S.S., 1991. Scintigraphic and pharmacokinetic assessment of a sustained release formulation of diltiazem. Int. J. Pharm. 76, 133–143.

Wilding, I.R., Sparrow, R.A., Davis, S.S., Horton, R.J., 1992a. The role of gastric emptying in the absorption and metabolism of nifedipine given in a modified release pellet formulation. Int. J. Pharm. 84, 59–69.

Wilding, I.R., Davis, S.S., Sparrow, R.A., Bloor, J.R., Hayes, G., Ward, G.T., 1992b. The effect of food on the in vivo behaviour of novel sustained-release formulation of tiaprofenic acid. Int. J. Pharm. 8, 155–161.

Williams, J., MacDonald, A., Weller, P.H., Fields, J., Pandov, H., 1990. Two enteric coated microspheres in cystic fibrosis. Arch. Dis. Childhood 65, 594–597.

Wilson, C.G., Washington, N., Greaves, J.L., Blackshaw, P.E., Perkins, A.C., Barkworth, M.F., Rehm, K.D., 1998. Wirkung der Vorbehandung mit Ranitidin auf Pharmakokinetik und gastrointestinale Passage eines Theophyllin Retard-Präparates. Arzneimittel-Forschung/Drug Research 48, 1154–1159.

Wilson, C.G., Washington, N., Greaves, J.L., Kamali, F., Rees, J.A., Sempik, A.K., Lampard, J.F., 1989. Bimodal release of ibuprofen in a sustained formulation: a scintigraphic and pharmacokinetic open study in healthy volunteers under different conditions of food intake. Int. J. Pharm. 50, 155–161.

Wise, D.L., 2000. Handbook of Pharmaceutical Controlled Release Technology. Marcel Dekker Inc., New York.

Yuen, K.H., Deshmukh, A.A., Newton, J.M., Short, M., Melchor, R., 1993. Gastrointestinal transit and absorption of theophylline from a multi-particulate controlled release formulation. Int. J. Pharm. 97, 61–77.