Expert Opinion

Gastric emptying of non-disintegrating solid drug delivery systems in fasted state: relevance to drug dissolution

Igor Locatelli, Nataša Nagelj Kovačič, Aleš Mrhar & Marija Bogataj†
†*University of Ljubljana, Faculty of Pharmacy, Askerčeva cesta 7, SI-1000 Ljubljana, Slovenia*

Importance of the field: Knowledge of gastric emptying (GE) of solid drug delivery systems (DDS) is meaningful for the development of new DDS as it enables the design of *in vitro* dissolution experiments with conditions close to those *in vivo* in order to predict drug plasma concentration profiles with high reliability.

Areas covered in this review: Gastric emptying of non-disintegrating pellets, tablets and mini-tablets in the fasted state is described on the basis of various studies performed in the last 30 years, which have evaluated the emptying process mostly by gamma scintigraphy. Different influences on GE and mathematical models describing GE kinetics of single and multiunit dosage forms are represented. A discussion on the implementation of these data in the development of drug dissolution testing procedures is given.

What the reader will gain: Readers will gain an insight into the kinetics and mechanisms of GE processes. Some suggestions on the use of the obtained knowledge in biopharmaceutical testing of DDS are also given.

Take home message: Gastric emptying of non-disintegrating solid DDS is a very important process, which might influence drug dissolution, bioavailability and the plasma concentration profile. It is reasonable to consider this process in biopharmaceutical testing of these DDS.

Keywords: drug dissolution, gastric emptying, non-disintegrating solid drug delivery systems, pellets, tablets

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1. Introduction

Solid dosage forms are the most frequently used drug delivery systems (DDS) for oral administration. They differ in size and number of units administered as a single dose, that is, single unit and multiunit DDS. Thus, solid dosage forms are usually used as tablets, as pellets that are most frequently incorporated in capsules or tablets, or sometimes also as mini-tablets. After administration the DDS moves along the gastrointestinal (GI) tract where it releases the drug. The conditions in various parts of the GI tract are different and as for many DDS drug release is dependent on these conditions, the transit times through different parts of the GI tract are very important. Namely, the kinetics of drug release might be changed in different parts of the GI tract and, consequently, in the case of different retention times different absorption kinetics and plasma concentrations might be expected for highly permeable drugs. Thus, it is very important to evaluate the kinetics of DDS transit through the GI tract and to implement this kinetics into the prediction of DDS behaviour in the GI tract by, for example, *in vitro* dissolution/release studies.

Different behaviour of DDS in different parts of the GI tract might be expected for DDS containing drugs, which are weak acids or basis and for which

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Article highlights.

- In this review, transport processes from stomach to duodenum for single and multiunit non-disintegrating DDS administered to healthy individuals in the fasted state are described on the basis of a literature review.
- The GE time of a single tablet is between a few minutes and 2 – 3 h, whereas pellets empty the stomach in a wide time interval ranging from a few minutes to > 3 h; emptying of pellets in a series of boluses was observed in several individuals.
- Gastric residence is prolonged at densities > 2.4 – 2.6 g/cm^3 for pellets and > 2.8 g/cm^3 for tablets, whereas size of the formulation might have an impact in the case of tablets.
- Mathematical models, most frequently the Weibull model, can be used to describe individual and mean GE profiles of pellets and GE of tablets in the population.
- The GE data can be implemented in *in vitro* dissolution testing procedures for DDS with release dependent on the conditions in the stomach and intestine, in order to increase the reliability of *in vivo* dissolution prediction.

This box summarises key points contained in the article.

the solubility and dissolution rate are dependent on pH value of the medium [1,2]. Also, some excipients may have pH-dependent solubility and dissolution as well. Consequently, the dissolution of many drugs from solid dosage forms is pH dependent in physiological pH range. There are also some other conditions in the GI tract that may provoke different behaviour of DDS in the stomach and intestine, such as the presence of physiological surfactants. That means that drug dissolution from these DDS will be different in gastric and intestinal media and that different retention times in gastric medium will give different drug dissolution profiles.

In dissolution testing procedures that are used today, at least two media are frequently applied: simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). In the cases when these two media are used consequently, the most frequently used residence time in SGF is 2 h, as stated in the pharmacopoeia for the delayed-release dosage forms [3]. The fact is, however, that performing a dissolution experiment at only one fixed time in SGF does not always reflect well the *in vivo* situation, either for multiple unit DDS, which empty the stomach over a wide time interval, or for a single unit system, for which one chosen time is correct only for some administrations.

This review is focused on the times needed for solid dosage forms to be emptied from the fasted stomach. Namely, gastric emptying kinetics is very important for many DDS [4], as for a large number of drugs absorption begins in the upper small intestine. Therefore, the authors aimed to collect and analyse all available literature data on gastric emptying of various solid dosage forms and to discuss the application of these data in planning the drug dissolution experiments. Among the selected studies, gamma scintigraphy was the most frequently used method to follow the gastric emptying of DDS [5], although the number of studies using magnetic marker monitoring is increasing [6-8]. On the other hand, the protocols of the selected studies were rather different; in some studies the factors that can markedly influence the GI transit were not well defined. Although the fasting conditions are well controlled, the provision of refreshments after the administration of a dosage form is very variable among the studies. This can be of a major importance because the refreshments with considerable caloric value might prolong the gastric emptying of solid dosage forms. Furthermore, in some studies the measurements were not performed frequently or long enough. With all this taken into account, a large variability between the studies can be expected. This should be borne in mind when evaluating the gastric emptying kinetics. Also, the kinetics of emptying of the stomach content under fasting conditions is very variable *per se,* as it is related to the activity of interdigestive migrating motor complex (MMC). A MMC cycle is ~ 2 h long and consists of four phases; Phase III is referred to be the 'housekeeper wave' owing to intense stomach contractions that are present in this short phase. Non-disintegrating solid dosage forms administered in the fasted state can be emptied from the stomach mainly during this phase [9]. As the DDS can be administered in any phase of the MMC cycle, the kinetics of the gastric emptying of solid dosage forms is very variable within the subjects as well as between the subjects.

This article is focused on the solid DDS, which empty the stomach after oral administration in accordance with physiological processes in the GI tract, that is, under fasting conditions the influence of MMC is the most important. However, prolonged gastric residence of modified release DDS is sometimes desired because it may increase drug bioavailability owing to prolonged absorption time. This could be relevant for drugs with an absorption window in the upper small intestine [10], osmotic pump tablets [11], and for other cases. In some cases this may be achieved simply by administration of DDS with food. On the other side, prolonged gastric retention of modified release DDS may sometimes reduce the drug bioavailability owing to the influence of drug first-pass metabolism [12], poor drug stability [10], and similar. Also, some formulations are able to escape basic physiologic principles of gastric emptying and prolong gastric retention as a result of their specific properties, such as floating ability, increase in size after contact with gastric medium, bioadhesive properties, and others. These so-called gastroretentive dosage forms have already been reviewed elsewhere [13-16] and are not included in this review.

In this review, transport processes from stomach to duodenum for single and multiunit DDS administered to healthy individuals in the fasted state are described. Also, the gastric emptying kinetics and mechanisms are compared, various influences are evaluated and the relevance to considering differences in these processes in drug dissolution evaluation is discussed. All descriptions and discussions relate only to

solid DDS, which do not disintegrate and their size in the stomach remains unchanged.

2. Gastric emptying of multiunit DDS

Pellets are spherical multiparticulate DDS that might be administered filled in a capsule, incorporated in a tablet or, less frequently, filled in sachets. The sizes of the pellets that were used in the gamma scintigraphic studies described below ranged from 0.5 to 1.8 mm in diameter. Only one study is an exception [17], where very large pellets (units of 4.75 mm in diameter) were compared with the smaller units (1.18 – 1.40 mm). However, the number of large units per administration was only four, which was substantially lower than the number of smaller units per administration [17]. When administered in the fasted state pellets leave the stomach over a wide time interval; the overall emptying time varies from a few minutes to ~ 3 h. Furthermore, several patterns of individual gastric emptying of pellets were observed: immediate and rapid, delayed followed by rapid, delayed followed by slow, and interruptive emptying [18,19]. The latter pattern, also described as emptying in a series of boluses, can be assigned to emptying of most pellets during the short periods of intense contractions of two consecutive MMC cycles (Phase III). The gastric emptying of pellets might also be influenced by other factors, such as the capsule disintegration time, the dispersion of the pellets in the stomach content, physicochemical properties of the pellets, the presence of food, and other physiological and pathophysiological conditions of the GI tract.

Owing to markedly different patterns of gastric emptying of pellets, it is difficult to quantify the kinetics of gastric emptying as a single parameter. The most common parameter used was the time for 50% of pellets remaining in the stomach (t_{50}); however, the use of this parameter alone was discouraged [20]. Instead, the application of statistical moments was introduced, and the use of parameters such as the area under the gastric emptying curve (AUC) and mean gastric residence time (MGRT) was proposed [20]. Presenting the gastric emptying kinetics of pellets with these parameters includes the whole emptying process, not just one specific time point as in the case of t_{50}. Also, the time when pellets started emptying the stomach (t_{lag}) was estimated in some studies [17,18,21,22].

The gastric emptying of pellets administered in the fasted state was examined by gamma scintigraphy in various studies. The first studies in this field were performed > 25 years ago. Christensen *et al.* [23] observed that regarding t_{50} values the gastric emptying of pellets (size 0.7 – 1.4 mm) coincided with the gastric emptying of a light meal; however, fasting conditions were not assured. Davis *et al.* [24] reviewed the gastric emptying of different dosage forms obtained from various studies. Solutions and small pellets (size: 0.3 – 1.8 mm) were found to be emptied from the stomach quite rapidly.

In later studies some new findings in relation to the pattern of gastric emptying of pellets were observed; moreover, the influence of pellets characteristics such as size and density on gastric emptying was investigated thoroughly. Devereux *et al.* [25] compared the gastric emptying of pellets (size: 1.0 – 1.4 mm) of two different densities (1.5 and 2.8 g/cm^3) in eight subjects, who were given both formulations on two different occasions. The mean (range) t_{50} values for gastric emptying were 125 (71 – 211) min and 204 (139 – 258) min for light and heavy pellets, respectively. The authors concluded that heavier pellets were retained in the stomach for a significantly longer time than the light pellets.

Clarke *et al.* [17] studied the influence of pellet size and density on gastric emptying. Four pellet formulations of two different sizes, 0.5 and 4.75 mm, and two densities, 1.5 and 2.6 g/cm^3, were administered to eight subjects on four occasions. A lag time in gastric emptying was observed for both small and large pellets. For small pellets the mean (range) t_{50} values were 125 (48 – 192) min and 141 (62 – 237) min for light and heavy pellets, respectively. On the other hand, the mean (range) t_{50} values for large pellets were 164 (74 – 281) min and 186 (69 – 307) min for light and heavy pellets, respectively. The gastric emptying was not affected by pellet size, however, significantly longer mean t_{50} values were found for heavier pellets (2.6 g/cm^3). The delayed gastric emptying of heavy pellets was explained by increased resistance to the contractions of the stomach. Also, heavy pellets might be trapped deeper in the gastric folds where they are protected against contractive activity of the stomach. One further study was performed by the same authors [18]. In this study the evaluation of gastric emptying of pellets (size: 1.2 – 1.4 mm) with three different densities (1.5, 2.0 and 2.4 g/cm^3) was performed in eight subjects on three occasions. Most gastric emptying curves showed some lag period, followed by rapid gastric emptying. Lag times were spread widely between the subjects, presumably owing to variability in the occurrence of Phase III of the MMC cycle. Also, three different patterns of pellets emptying were observed in one particular subject; delayed and followed by rapid emptying, delayed followed by slow emptying, and interruptive emptying. In the explanation of these patterns of pellets emptying, the authors concluded that the emptying of pellets appeared to occur quite independently of liquid emptying [18]. The mean (range) t_{50} values 185 (98 – 477) min, 186 (79 – 261) min and 168 (1 – 279) min were obtained for pellet densities 1.5, 2.0 and 2.4 g/cm^3, respectively. No significant prolongation of gastric emptying of pellets of these densities was indicated. Comparing these results with their previous study Clarke *et al.* [17], suggested that there might be a threshold density of the order of 2.4 – 2.6 g/cm^3, above which gastric emptying of pellets is prolonged.

Wilding *et al.* [26] investigated the transit of microgranules through the GI tract in eight healthy subjects who received either intact microgranules (dosed in a sachet) or microgranules compacted into tablets. The mean (range) t_{50} values for gastric emptying of the microgranules were 22 (10 – 38) min and 17 (8 – 20) min dosed in the sachet and tablet, respectively. They concluded that the gastric emptying of

the microgranules was rapid irrespective of the dosage form used, suggesting that tablets disintegrated quickly in the stomach and the microgranules entered the duodenum shortly after dosing.

The influence of subject's posture on gastric emptying of pellets was also investigated; however, in most studies investigating the gastric emptying of pellets under fasting conditions the subject remained in an upright position during the evaluation. Khosla and Davis [27] found no significant difference in mean t_{50} values when pellets (size: 0.5 – 1.0 mm, density: 1.17 g/cm^3) were administered to five volunteers on two occasions; on the first occasion the volunteers were lying in a supine position and in the second they remained upright. In another study [21], two subjects (one in an upright position and the other in a supine position) were given pellets (size: 0.7 – 0.85 mm, density: 1.2 g/cm^3). The gastric emptying in the supine subject was markedly shortened; however, no firm conclusions could be drawn based on only one measurement. Nevertheless, the question whether the supine position of subjects under fasting conditions influences the gastric emptying rate of pellets remains open.

The mechanism and kinetics of gastric emptying of pellets under fasting conditions were evaluated in a study by Locatelli *et al.* [19]. On the basis of the gastric emptying data that were obtained from several studies performed on healthy volunteers under fasting conditions [17,18,21,22,25,27-33], a mathematical model describing different emptying patterns of pellets was developed. The interruptive emptying of pellets was described by the double Weibull model, whereas mean gastric emptying of pellets was represented by the Weibull model. The latter model, referred to power exponential model, was also applied in the analysis of the gastric emptying data in the study by Elashoff *et al.* [34].

3. Gastric emptying of single unit DDS

Tablets are single unit dosage form with various sizes and shapes. The diameter of round tablets that were used in the studies described below, investigating gastric emptying, was between 6 and 13 mm. On the other hand, the length of oval tablets or capsules was from 10 to 21 mm with the width ranging from 5 to 7 mm. The non-disintegrating tablets and capsules are emptied from the stomach at a certain time point – often referred as the tablet gastric emptying (GE) time. In most of the studies the GE times of tablets were assessed using gamma scintigraphy. Podczeck *et al.* [35] estimated the maximum length of the image acquisition interval still suitable for monitoring the emptying of single unit DDS using gamma scintigraphy. Accordingly, image acquisition intervals no longer than 3 min should be chosen, whereas intervals < 1 min are not appropriate because it takes 30 s to take a high-quality scintigraphic image.

Under fasting conditions the tablet GE time is very variable, from a few minutes up to 2 – 3 h after administration. This depends on the phase of MMC cycle occurring at the time of tablet administration. Namely, the tablet can leave the stomach only in Phase III of ~ 2 h long MMC cycle. Thus, it probably remains in the stomach until the first Phase III appears provided that the MMC is not interrupted by food intake. The gastric emptying of tablets might also be influenced by other factors, such as the physicochemical properties of the tablets (for example, size, shape, density, excipients), the presence of food, and other physiological and pathophysiological conditions of the GI tract.

Kaus *et al.* [36] studied the influence of capsule density on GI transit of non-disintegrating hard gelatine capsule in four healthy subjects. Each subject received one capsule with 200 ml of orange juice on four occasions (two replicates). The ranges of GE times were 21 – 197 min for lighter capsules (specific gravity 1.03 ± 0.02) and 15 – 190 min for heavier capsules (specific gravity 1.61 ± 0.02). No significant influence of capsule density on capsule GE time was noted.

Sangekar *et al.* [37] studied the influence of tablet density on GE time in a crossover study performed in two parts consisting of four subjects in each part. In the first part the subjects received a floating tablet (specific gravity 0.96) under either fasted or fed conditions, whereas in the second part the subjects simultaneously received both floating and non-floating tablets (specific gravity 1.59) under both feeding conditions. When administered in the fasted state the mean (range) values of tablet GE times from the second part were 132 (76 – 177) min for floating tablets and 152 (90 – 229) min for non-floating tablets. Sangekar *et al.* concluded that under fasting conditions tablets' specific gravity did not significantly affect the GE time.

In one study Davis *et al.* [38] examined the gastric emptying of floating tablets (1.25 g/cm^3, floating properties resulting from the formation of a gel layer, ^{99m}Tc) and hard gelatine capsules (floating system containing a mixture of sodium alginate and sodium bicarbonate, ^{113m}In) and non-floating tablets (1.2 g/cm^3, ^{99m}Tc) in the fasted state. On one occasion a floating tablet and floating capsule were administered concurrently to four fasted subjects, whereas on the second occasion a floating capsule was administered to other four fasted subjects together with a non-floating tablet. The mean (range) values of GE times were 49 (17 – 75) min for floating tablets and 60 (30 – 90) min for floating capsules. On the second occasion the ranges of GE times obtained were 75 – 420 min for floating capsules and 75 – 120 min for non-floating tablets. No significant differences in gastric emptying time of the floating and non-floating systems were observed.

Podczeck *et al.* [35] studied the influence of tablet density on gastric emptying times in seven fasted subjects, each of whom received at the same time a light (1.50 g/cm^3) and a dense tablet (3.70 g/cm^3). Both tablets were round and of the same size (diameter: 12.2 mm). The median (range) values of tablet GE times were 14.8 (11 – 66) min for light and 24.6 (14 – 74) min for dense tablets. Podczeck *et al.* urged the use of non-parametric statistical tests; with the Wilcoxon signed-rank test a significant difference between

light and dense pellets was noted if the image acquisition intervals were 3 min or more frequent ($p = 0.018$). On the other hand, the results based on the parametric t-test did not lead to the same conclusions. The same authors expanded this research by examining the influence of tablet density on smaller round tablets (diameter: 6.6 mm) [39]. In this study, eight fasted subjects received at the same time a light (1.41 g/cm^3) and a dense tablet (2.85 g/cm^3). The analysis with Wilcoxon signed-rank test revealed that tablets with higher density had significantly ($p = 0.043$) longer tablet GE times (median: 82.0 min, range: 23 – 181 min) than those with lower density (median: 58.0 min, range: 37 – 540 min). The authors also compared the results obtained with those from previous study [35]. They concluded that 12.2 mm tablets emptied the stomach faster than 6.6 mm tablets, suggesting that the pyloric sphincter does not control the dimensions of the object that leaves the stomach. Also, it was postulated that the effect of tablet size outweighed the effect of density.

Park *et al.* [40] explored the gastric emptying of tablets of different size and shape. Six different tablets of various shape and size were given to six subjects on seven occasions (one tablet on each occasion). The diameters of small, medium and large sphere-shaped tablets were 6.0, 9.5 and 12.7 mm, respectively, whereas the lengths of small, medium and large capsule-shaped tablets were 9.8, 13.0 and 17.6 mm, respectively. All the subjects received medium sphere-shaped tablets on the seventh occasion. The tablets left the stomach unpredictably and no firm connection between tablet size or shape and tablet GE times could be concluded. On 12 recordings the imaging was abandoned before the tablets were emptied from the stomach, and the estimation of exact tablet GE time data was impossible. The tablet GE times ranged from 5 to > 140 min.

Davis *et al.* [41] evaluated the GI transit of a controlled release tablet formulation (17 × 4 mm dimension) in six young and six old subjects under either fasted or fed conditions. The mean (range) values of the tablet GE times were 0.86 (0.4 – 1.6) h and 0.64 (0.4 – 1.2) h for old and young fasted subjects, respectively. Using a non-parametric Mann-Whitney test, no significant differences in GE times between the age groups were observed.

In some studies the subjects concurrently received several tablets. In such cases the tablets' GE time was usually defined as the time when 50% of the tablets or 50% of the gamma-emitting activity remained in the stomach. Adkin *et al.* [42] examined the gastric emptying of five tablets of different sizes. Each of the eight subjects was given five round tablets (diameter: 6 mm, ^{111}In) and another five round tablets of various diameter size (3, 9 or 12 mm, all marked with ^{99m}Tc) on three occasions. The mean (standard deviation) values of GE times for 6 mm tablets measured on three occasions were 36 (32) min, 24 (15) min and 53 (57) min. Mean (standard deviation) values of GE times for 3, 9 and 12 mm tablets were 38 (33), 54 (59) and 51 (52) min, respectively. The authors noted that no pattern of gastric emptying of these tablets can be concluded, the five tablets emptied neither as a bolus nor individually. The size of the tablets appeared to have no influence on tablets' GE times. In one study (study III) Sugito *et al.* [43] investigated the influence of tablet density on gastric emptying. Four non-disintegrating light tablets (relative density 0.86, diameter 10.0 mm, ^{111}In) and four non-disintegrating heavy tablets (relative density 1.33, diameter 8.0 mm, ^{99m}Tc) were simultaneously administered to four fasted subjects. The mean (range) values of tablet GE times were 0.6 (0.3 – 1.3) h for heavy and 0.7 (0.3 – 1.5) h for light tablets. The results indicated that under fasting conditions tablets' relative density did not significantly affect the GE time. Khosla and Davis [44] studied the GI transit of five non-disintegrating tablets (diameter 5 mm) in five fasted subjects after repeated administration on three consecutive days. The mean (range) values of tablets GE times were 25 (10 – 35) min, 30 (10 – 50) min and 113 (43 – 230) min measured on the three consecutive days. A lag time in gastric emptying of ~ 200 min was noted in one of the subjects on the third day of the study. Wilding *et al.* [45] evaluated the GI transit of a capsule containing four Geomatrix round tablets in eight subjects on two separate occasions, in fasted and fed state. The mean (range) value of the tablets' GE time under fasting conditions was 52 (7 – 250) min. Also, a wide emptying interval was observed and attributed to MMC movement of the stomach.

The modelling of tablets' GE data under fasting conditions was presented in the study by Locatelli *et al.* [46]. The population data involving GE times of non-disintegrating single unit DDS that were collected from several studies in the literature were represented by the Weibull model. The use of the Weibull model for describing tablets' GE data was also proposed by Jamei *et al.* [47].

4. Gastric emptying of mini-tablets

Pellets and tablets differ according to their size, shape and the number of units per administration. In some cases the DDS consists of a small number of little tablets, also called mini-tablets. In the studies investigating the gastric emptying of mini-tablets, four to six round mini-tablets per administration were used. The diameter of the mini-tablets was smaller than the diameter of single unit round tablets; in the studies presented, mini-tablets of 3 – 5 mm diameter were used. The kinetics of gastric emptying of tablets or pellets cannot be directly applied to mini-tablets. Although under fasting conditions the mini-tablets empty the stomach according to MMC activity, no unified pattern of their emptying was identified. Mini-tablets may leave the stomach individually or as a group of a few units in several boluses, or also as one bolus. All these mechanisms are discussed in the literature, although it is not always possible to monitor each unit separately. Furthermore, the evaluation of gastric emptying data is also debatable. Owing to the small number of units the use of parameters such as t_{50} or MGRT does not seem to be appropriate [48]. However, the time when 50% of units leave the stomach is still

widely used. Another approach for evaluating gastric emptying of mini-tablets is to determine the time of gastric emptying of the first and the last mini-tablet and to report the difference as the GE interval.

In some studies reported in this review the tablets of smaller size were administered simultaneously as several single units; however, this was not considered as a potential DDS, it was rather a consequence of specific study design [42-45]. The results of these studies are given in Section 3. The studies listed below describe the kinetics of gastric emptying of mini-tablets under fasting conditions.

Podczeck *et al.* [48] examined the influence of mini-tablet density on gastric emptying times in eight fasted subjects; each of them concurrently received five light (1.38 g/cm^3, ^{111}In) and six dense (2.86 g/cm^3, ^{99m}Tc) round non-disintegrating mini-tablets of size 3.2 mm. The time of the first and the final emptying was recorded and the corresponding emptying period was estimated. The emptying times for the first light mini-tablet (median: 94 min, range: 23 – 177 min) were significantly shorter than those for the first dense mini-tablet (median: 156 min, range: 38 – 218 min) as revealed from the non-parametric Wilcoxon signed-rank test ($p = 0.012$). No significant differences were observed when the other two gastric emptying times were compared. The median (range) values for the emptying period were 38 (13 – 185) min and 28 (4 – 178) min for the light and dense mini-tablets, respectively. The authors also compared the results of this study with the results obtained from their previous studies [35,39]. Accordingly, the times of the first emptying of mini-tablets were longer than GE times of larger single unit tablets (diameter 6.6 and 12.2 mm). Damle *et al.* [49] compared the GI transit of three different dosage forms (encapsulated enteric coated beads, four enteric coated mini-tablets of 5 mm diameter, and chewable tablet) in the fasted state. A three-way crossover study in 18 subjects was performed, each subject receiving each dosage form on a separate occasion. The mean values of the GE time (time for 50% of radioactivity remaining in the stomach) and the first emptying time (time for < 95% of radioactivity remaining in the stomach) of four mini-tablets were 0.50 and 0.55 h, respectively.

5. Comparison of the gastric emptying of pellets and tablets

Under fasting conditions, the gastric emptying of both single and multiunit depends on MMC activity in the stomach. However, this dependence is expressed more in the case of emptying of a non-disintegrating tablet, which empties according to an all-or-nothing principle. On the other hand, pellets are emptied from the stomach in a wide time interval. Thus, the gastric transit of a tablet and pellets in an individual is very hard to compare. It is not possible to make any conclusions about gastric transit times being longer or shorter for tablets in comparison with pellets; but when comparisons of the gastric transit and anticipation of drug absorption and plasma concentration profiles in an individual are necessary, the gastric emptying pattern of both formulations has to be considered. Typical individual gastric emptying patterns of a tablet and pellets administered under fasting conditions are presented in **Figure 1A**.

Although the individual emptying pattern of pellets is quite different in comparison with the tablet, the decreasing cumulative distribution curve of GE times of tablets is quite similar to the mean gastric emptying profile of pellets (**Figure 1B**). Both of these profiles illustrate the gastric emptying kinetics of each DDS in the population and can be described by the Weibull distribution function [19,46]. The mean gastric emptying of pellets is a bit slower in the last part of the emptying process. This could be attributed to the small fractions of pellets, which rest in the stomach longer than one MMC cycle, as observed in some individuals [19].

The gastric emptying data of single and multiple unit DDS under fasting conditions have been directly compared in several studies. Davis *et al.* [50] compared gastric emptying of a tablet and pellet formulation concurrently administered in a group of six subjects; however, the fasting conditions were assured in only one subject. The pellets' t_{50} values were compared with the GE time of the tablets. In fasted subjects, rapid gastric emptying of pellets (t_{50} = 33 min) as well as of the tablet (GE time = 42 min) formulation was observed. Also, the authors noted that the pellets spread a little within the stomach. Hardy *et al.* [29] compared the GI transit of multiple unit system and a non-disintegrating radiotelemetry capsule in a group of six subjects. The pellets and the capsule were administered together and emptied from the stomach at about the same rates. Median t_{50} value for pellets and GE time for the capsule were 1.2 and 0.8 h, respectively. Brunner *et al.* [51] compared the GI transit of a pellet and tablet formulation in 14 subjects in randomized crossover design. They reported the results for both formulations as gastric emptying and the mean (standard deviation) values were 0.94 (0.70) h for pellets and 0.56 (0.71) h for tablets.

6. Conclusion

The gastric emptying of single and multiunit solid DDS is an important process, which might influence the drug plasma concentration profiles, especially in the cases when dissolution from DDS is different in the stomach compared with the small intestine. Gastric emptying of all solid non-disintegrating DDS administered in the fasted state is dependent on MMC; however, this dependence is expressed more in the case of tablets. Pellets empty the stomach in a time interval ranging from a few minutes to > 3 h; in several individuals emptying in a series of boluses according to MMC can be observed. The GE time of a single tablet is between a few minutes and 2 – 3 h. In this review the gastric emptying of mini-tablets has also been considered. Concerning the gastric emptying pattern of the mini-tablets, it is noted that mini-tablets may leave the stomach individually or as a group of a few units in several boluses, or

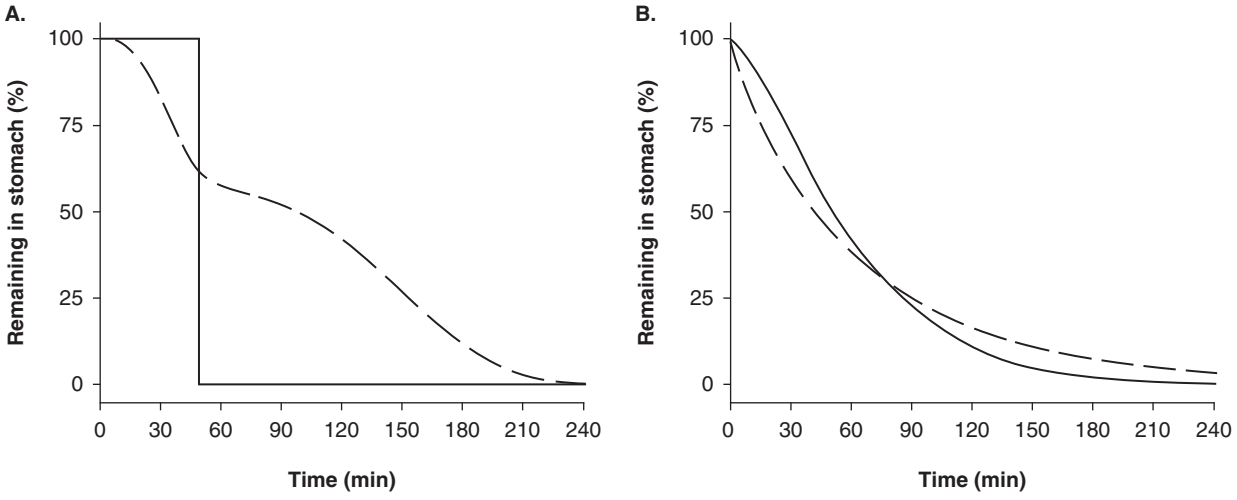

Figure 1. Comparison of gastric emptying of pellets and tablets under fasting conditions. A. Typical individual gastric emptying of a tablet (unbroken) and pellets (dashed). **B.** Cumulative distribution of gastric emptying times of tablets (unbroken) and mean gastric emptying profile of pellets (dashed) described by the Weibull model.
Adapted from [19,22,46].

also even as one bolus. In the studies discussed in this review, two of the most important properties of DDS that can influence the gastric emptying are the density and size of the formulation. In this view, in some studies it is concluded that pellets with high density (> 2.6 g/cm^3) remain in the stomach for a longer period than the pellets with lower density. The GE times of the tablets with very high density (> 2.8 g/cm^3) are also significantly longer than the times of the tablets with usual density. In the case of tablets' size, the situation is less clear. A comparison of three studies performed by the same authors showed that larger tablets empty the stomach faster than smaller tablets, whereas in two other studies no difference in GE time of tablets of various sizes was found. For some other factors such as the subject's posture and age, very few studies have been performed, and no firm conclusions can be made regarding the influence of these factors.

7. Expert opinion

This review includes a large number of individual studies, which express a high degree of variability in their protocols and results obtained. However, various influences have been studied, mostly in the scope of single studies, that is, under the same conditions, and are, in the authors' opinion, quite reliable, especially when confirmed in several studies. On the other side, the mathematical models describing the kinetics of gastric emptying [19,46], which were developed on the basis of a larger number of studies, include all variability of the data from these studies. With the aid of these models, gastric emptying kinetics can be implemented in dissolution testing of the DDS, whose dissolution is highly dependent on the conditions in the stomach and small intestine. This can be performed by designing the dissolution experiments at several retention times in SGF. On the other hand, performing dissolution experiments at only one time in SGF has been used so far. Pellets or tablets with drug dissolution dependent on pH or other GI conditions will release the drug at a different rate if their retention in the stomach is changed. Also, in the case of highly permeable drugs different absorption and plasma concentration profiles are expected. The fact is that *in vitro* testing at a single retention time in SGF cannot predict well the absorption profiles in these cases. For pellets, the dissolution profile performed at only one retention time in SGF would represent the dissolution kinetics of only a limited portion of pellets. For tablets, such a dissolution profile would represent the *in vivo* situation only in a limited number of cases, that is, when the tablet is emptied from the stomach at the same time as used in the dissolution experiment. Thus, designing the dissolution tests at several retention times in SGF, before changing to SIF, was suggested for pellets [19] and tablets [46]. From these profiles the mean *in vitro* dissolution profile can be calculated considering the contribution of each dissolution profile determined on the basis of the gastric emptying model.

The purpose of *in vitro* dissolution experiments is also to predict *in vivo* dissolution of the drug. But does the profile obtained considering several retention times in SGF simulate the *in vivo* situation well for all solid dosage forms? In general, the answer is affirmative for DDS with drug release dependent on various conditions in the stomach and small intestine; however, the situation is different for single and multiunit dosage forms.

In an individual, a tablet is emptied from the stomach at a single time point. So, the *in vivo* dissolution profile in

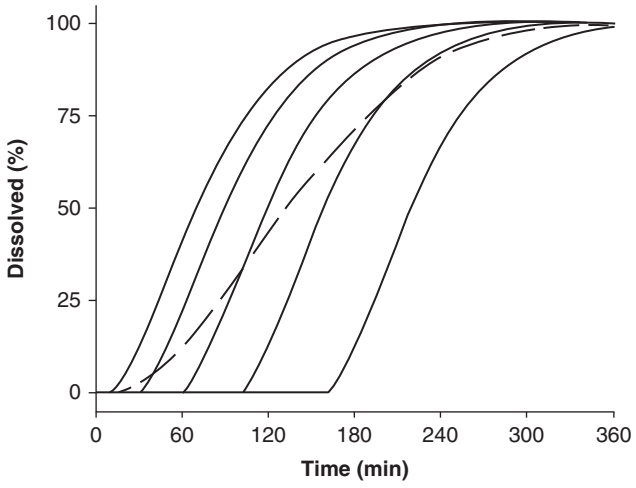

Figure 2. Hypothetical *in vitro* drug dissolution profiles from enteric coated pellets (unbroken) and prediction of population *in vivo* dissolution profile based on the mean gastric emptying profile (dashed).

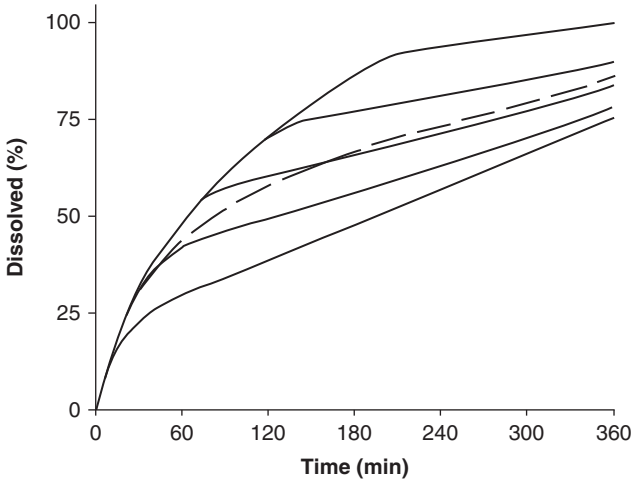

Figure 3. Hypothetical *in vitro* drug dissolution profiles from pellets with higher dissolution rate in gastric than in intestinal medium (unbroken) and prediction of the population *in vivo* dissolution profile based on the mean gastric emptying profile (dashed).

the individual can be predicted properly by dissolution determination at only one single residence time in SGF. It is not known in which MMC phase the stomach is at tablet administration; consequently, it is not known how long the tablet will remain in the stomach. Thus, the whole family of potential individual dissolution profiles can be obtained on the basis of several residence times in SGF. The individual *in vivo* dissolution profile is expected to be the same as one of these profiles. Also, on the basis of dissolution profiles performed at several retention times in SGF and the kinetics of gastric emptying of tablets in the population, the mean dissolution profile can be calculated. This profile can give good prediction of population *in vivo* drug dissolution from tablets.

Introducing the principle of different residence times in acidic medium into dissolution testing of pellets will certainly implement the pellets' gastric emptying process better than testing at only one residence time as pellets usually leave the stomach over a wide time interval. The mean dissolution profile can be calculated considering both gastric emptying and drug dissolution. By establishing the mean gastric emptying profile [19] the population mean dissolution profile can be calculated. On the other hand, the individual mean dissolution profile cannot be calculated as particular individual gastric emptying kinetics is not known. However, on the basis of typical individual gastric emptying profiles obtained from the literature, typical individual mean dissolution profiles can be determined.

Enteric formulations are typical DDS, whose behaviour in the stomach and small intestine differ significantly. In **Figure 2**, *in vitro* dissolution profiles from enteric coated pellets determined at several residence times in SGF are simulated. The contribution of each dissolution profile was determined on the basis of the mean gastric emptying profile [19], and the mean dissolution profile, which represents predicted *in vivo* dissolution profile for the population, was calculated. Another example of DDS with different drug dissolution rate in the stomach in comparison with the small intestine is presented in **Figure 3**. Here, the simulated drug dissolution profiles from pellets, which release the drug faster in the gastric than in the intestinal medium, are shown. Such dissolution profiles might be the consequence of different solubility of basic drugs in the gastric and intestinal media or specific properties of excipients. In **Figure 3**, *in vitro* dissolution profiles determined at several retention times in SGF are shown together with the calculated mean profile, which represents the predicted *in vivo* dissolution profile for the population. On the basis of the model of gastric emptying of tablets in the population and tablets' *in vitro* dissolution profiles, the principle described above can also be applied to prediction of population *in vivo* drug dissolution from tablets.

In the scope of this review, the emphasis has been placed on the relation of drug dissolution kinetics and kinetics of gastric emptying. However, when predicting *in vivo* dissolution profiles on the basis of *in vitro* dissolution, many other physiological parameters might influence the reliability of this prediction, for example, the transport rate of the drug released in the stomach to the absorption site, water availability in the lumen of different parts of the GI tract [52], the influence of mechanical forces [53], and others. Yet it is difficult to define to what extent each influence will be expressed in a certain case. The suggested approach can predict *in vivo* behaviour of DDS well in the cases when

the impact of gastric emptying prevails over other physiological influences. However, the use of the approach described above has to be justified and the suitability should be confirmed by good *in vitro/in vivo* correlations.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Affiliation

Igor Locatelli[2] MPharm PhD,
Nataša Nagelj Kovačič[3] MPharm,
Aleš Mrhar[4] MPharm PhD &
Marija Bogataj[†1] MPharm PhD
[†]Author for correspondence
[1]Associate Professor,
University of Ljubljana,
Faculty of Pharmacy,
Aškerčeva cesta 7, SI-1000 Ljubljana,
Slovenia
Tel: +386 1 4769 500; Fax: +386 1 4258 031;
E-mail: marija.bogataj@ffa.uni-lj.si
[2]Assistant Professor,
University of Ljubljana,
Faculty of Pharmacy,
Aškerčeva cesta 7, SI-1000 Ljubljana,
Slovenia
[3]University of Ljubljana,
Faculty of Pharmacy,
Aškerčeva cesta 7, SI-1000 Ljubljana,
Slovenia
[4]Professor,
University of Ljubljana,
Faculty of Pharmacy,
Aškerčeva cesta 7, SI-1000 Ljubljana,
Slovenia