SYSTEMATIC REVIEW

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The Role of Sphere Size in the Context of Pancreatin Therapy for Exocrine Pancreatic Insufficiency: A Systematic Review

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ABSTRACT

While lipase content and appropriate acid protection of pancreatin preparations (PP) are well defined determinants of an effective therapy of exocrine pancreatic insufficiency, the optimal sphere size of PP has remained a matter of discussion. We performed a systematic review to assess the optimal sphere size of enteric coated pancreatin products that may best guarantee coordinated delivery of PP and food to the duodenum. PubMed was searched for studies on gastric emptying of indigestible spheres in the digestive phase, using overlapping search algorithms; identified sources were searched for further leads, extending the investigation to Google Scholar. Of 739 screened publications, 26 were included in the final assessment. Contrary to current guideline recommendations, no scientific evidence was found to support a 2 mm diameter threshold for gastric emptying of indigestible particles. There is no documented advantage of ≤2 mm spheres regarding duodenal delivery and restoring maldigestion. The evolving picture is that of a gradation of sizes, over which gastric emptying becomes slower and more variable as particle size increases. Even 7 mm particles may be emptied from the stomach in conjunction with nutrient uptake. In conclusion sphere size of PP is not the essential parameter for selecting an effective PP fitting all patients. A variety of brands offer different lipase contents and sphere sizes that allow the physician to tailor treatment to the individual patient`s needs.

Key words: pancreatin – pancreatic insufficiency – sphere size – gastric emptying.

Abbreviations: PEI: pancreatic exocrine insufficiency; PP: pancreatin preparations.

INTRODUCTION

In treatment of pancreatic exocrine insufficiency (PEI), substitution of pancreatic enzymes with pancreatin preparations (PP) has become standard clinical practice in the past century [1, 2]. Currently available PP differ significantly in their enzyme content, the presence or absence of enteric coating, and the size of spheres. Major uncertainty has remained concerning the most suitable sphere sizes of multiple-unit PP in patients with intact gastroduodenal anatomy and preserved pylorus function. Upper limits of sphere size have become a claim for optimal, i.e., food-aligned passage to the duodenum, some reviews citing a threshold of 1.4 mm [3, 4], and guidelines recommending a sphere diameter of ≤ 2.0 mm [5, 6]. The medical literature on the relation between the size of pancreatin spheres and their gastric emptying during the postprandial phase reports discrepant results.

The pylorus marks the gastroduodenal junction and controls the timely and orderly delivery of the chyme to the duodenum, integrating signals from a variety of vagal and non-vagal neurons, hormones and neurotransmitters [7, 8]. The opening diameter of the pylorus differs significantly between the fasting (interdigestive) and postprandial state. Dependent on the method, values of, e.g., 5-10 mm (mean, 8.7 mm) [9] and about 13 mm [10], have been reported for the interdigestive phase with migrating motor complexes. In the digestive phase, the pylorus is a closed gate with defined intermittent openings, a state that supports the gastric milling of solid food to particles of 1-2 mm [11]. Intermittent openings to a width of 2-3 mm [12] are instrumental in passing 2-4 ml portions of suspended particles into the duodenum [11].

Even so, it seems that larger particles can still pass the pylorus in this state, being squeezed through in perhaps a two-step process. This may be understood by a look at local anatomy. The pyloric segment in humans consists of two circular muscle loops [7]. Closure is performed by contraction of these loops, occlusion being completed by mucosal folds projecting into the pyloric lumen [8]. This arrangement alone makes identifying a distinct size of the aperture an ambitious undertaking and will, with the right propelling force, still allow passage of particles larger than the nominal aperture.

There is no uniform rate descriptor of gastric food emptying. Rather, individual characteristics and the properties of the meal determine the rate at which the chyme is released to the duodenum. The food's caloric content is the predominant factor, with fat components exerting some retarding modulation [13-15]. Liquids are emptied in two phases. Phase one has an immediate onset when solid food is still retained, followed by phase two with simultaneous emptying of liquid and solid food [16]. Solutions [17-19] and solid meals [20] of lower caloric content empty fastest. Emptying of solid food is delayed by the period of time needed to mill it to the appropriate size, which, e.g., takes longer for 25 than 10 mm liver cubes [21]. A further level of complexity is added in that chyme is not a homogeneous suspension. Notably, oil has been observed to show phase separation, leading to layering of fat above water [13]. *In vitro* experiments revealed that indigestible spheres aggregated in the oil phase [22]. Thus, dietary fat, whether liquid or solid at body temperature, is rapidly cleared from the stomach in the first postprandial hour and slowly later on [23], while the aggregates will stay behind, irrespective of their constituents´ original size.

We carried out a systematic review, with the intention to provide an evidence-based understanding of the importance of sphere size in treatment of pancreatic insufficiency with PP.

METHODS

In a systematic review of PubMed, search terms were selected to identify literature on gastric emptying of indigestible particles of different sizes in volunteers or patients with PEI under fed conditions. Seven different search algorithms were used, combining a variety of pertinent terms in different arrangements (Supplementary file, Table SI). A total of 1,052 studies were retrieved, plus 16 studies derived from review articles. Fig. 1 delineates the workflow from the initial searches to the 26 studies ultimately included in the analysis, in accordance with PRISMA guidelines [24]. The identified studies are summarized and commented upon in Tables SII and SIII of the Supplementary file.

Eligible studies allowed a comparison between different particle sizes or, where only a single size was explored, to put this in perspective with emptying of food taken with the particles. Animal studies were disregarded, as were studies concerned with drug effects and PK, effects of neuropeptides/gastrointestinal hormones, specific drug formulations, drugs targeting the lower intestine, or peculiarities of health disorders like diabetes, Parkinson´s disease, and non-ulcer dyspepsia. Moreover, studies relying on the appearance of urinary markers for assessment of gastric emptying or being restricted to fasted persons or liquid meals were excluded.

Twenty-two of the final 26 studies reported data from 5–14 subjects; 20 persons were included in 3 studies [25-27] and only two studies had enrolled more than 20 (26 and 56) individuals. However, the two larger-size studies were subdivided in treatment groups of no more than ten subjects [28, 29]. Because of the high diversity of study designs and techniques, no attempt was made to lump any results or to weight data by study size.

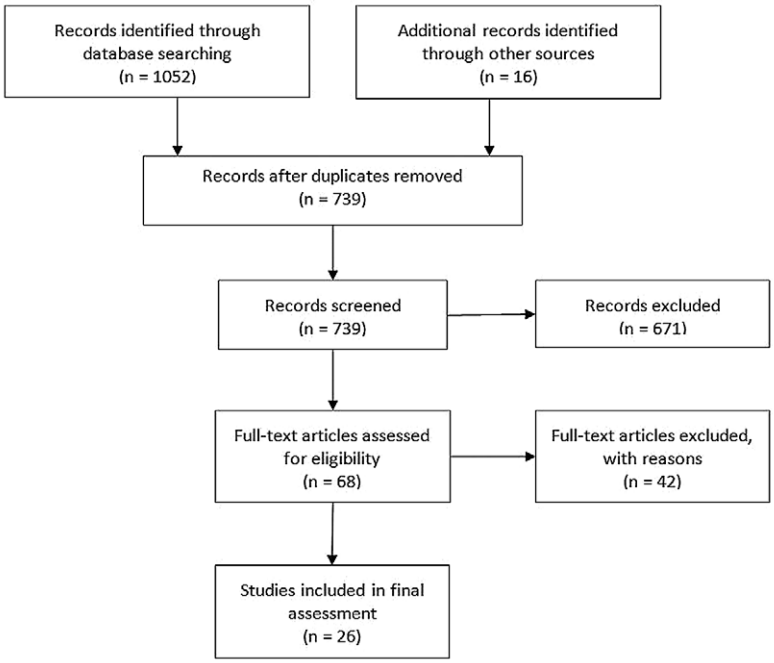

Fig. 1. Workflow of identification of studies relevant to the determination of the appropriate size of pancreatin spheres.

After the deletion of duplicate findings, the remaining abstracts were screened independently by two authors in varying combinations. The few discrepancies identified by the third author were resolved by consensus of all authors.

Each of the authors meets the criteria for authorship established by the International Committee of Medical Journal Editors and verifies the validity of the results reported.

RESULTS

Systematic review of transpyloric passage of indigestible particles

Cut-off size

There has been an (elusive) quest for the size of a particle that would block its pyloric passage in the fed state. While the textbook value for milled food particles of 1-2 mm is persuasive to suggest a comparable size requirement, a higher limit is supported by or consistent with 20 of the 26 studies listed in Tables S1 and S2 of the Supplementary Material. These studies suggest that, beyond a certain particle size, pylorus passage slows down and becomes more variable. This transitional range may start at diameters of 3–3.6 mm, but particles of perhaps up to a diameter of 5-7 or even 11 mm can still pass in the digestive phase, although with a sizable inter-individual heterogeneity [30, 31]. This is illustrated in Fig. 2 for the study by Coupe et al. [30] (Table I, line 10). In contrast are two studies [32, 33], where the authors concluded that 2 mm diameter spheres emptied in the interdigestive phase, and second, studies that relied on liquid rather than solid test meals [34-36].

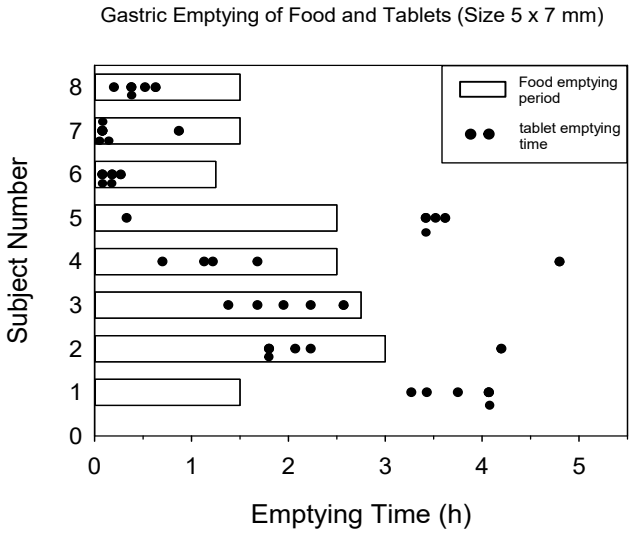

Fig. 2. Period of gastric emptying of a radiolabelled egg meal in relation to emptying of 5 labelled tablets sized 5x7 mm (according to data from [30]).

The unfolding picture conforms to that given by Yamada et al. [37], who summarized that spheres <3 mm in diameter can pass into the intestine during the fed period, whereas larger spheres pass more slowly, often after a lag period, and, moreover, that spheres greater than 7 mm in diameter do not empty with a digestible solid meal.

Temporal relationship with food emptying in healthy persons

Of particular relevance is the temporal relationship between gastric emptying of spheres of a given size and that of food. As too early an arrival of the drug might compromise proper fat digestion, porcine extracts are usually applied together with the meal or shortly thereafter, when most of the chyme is still present in the stomach. However, gastric motility is influenced by chronic pancreatitis, resulting in delayed or even shortened gastric emptying [38].

Results considered in this section are summarized in Table I; more details, enhanced by comments, are available in Table SII of the Supplementary File. Perhaps because of the perceived 2 mm limit, a particle length or diameter of 2 mm has been selected in a number of gastric emptying studies (Supplementary File, Table SII). Bruno et al. [39] reported that gastric transit of 2 mm pancreatin spheres lagged behind that of a pancake meal (Table I, line 9). Most interestingly, this relation was reversed in patients with PEI. Several authors favoured particles with unequal side lengths or heights (Table I, lines 5, 7, 8, 12-15). Intuitively, such particles may leave the stomach aligned lengthwise with the pylorus, and indeed this has been shown for indigestible cylinders, sized 2x5 mm [27]. This means that the smallest extension determines the emptying time, which may be extended by the period required for longitudinal adjustment. Feldman et al. [32], comparing gastric emptying of 2x10 mm tubes and labelled egg, concluded that most markers left the stomach in the interdigestive phase. A follow-up study [33] found no difference between 2x2 and 2x10 mm tubes, with or without a meal, and reached the same conclusion. Brogna et al. [40] reported that gastric emptying of indigestible (2x5 mm) and digestible solids occurred simultaneously, though with a slight temporal advantage of the food at 120 min. Similarly, Loreno et al. [27] reported simultaneous emptying of particles (2x5 mm) and food, that was indistinguishable at 120 min post-intake.

Not pertinent to the current topic is a study, in which 2 mm spheres taken with a liquid meal were investigated [36] (Table 1, line 15). This strategy obviates a relevant comparison between food and pellet emptying, given the facts that liquids per se empty faster than solid food and that pellets clear the stomach only after a lag time when administered with a liquid. Such lag times were found to be similar for pellets with diameters of 0.5 and 4.75 mm [34].

Results with larger particles (3 mm diameter or length) are no less disparate than those with smaller ones (Supplementary File, Table SII). Bruno et al. [39] cited examples of 3 mm particles emptying, relative to a solid meal, faster, slower, or at similar rates. Of these studies, two reporting on 3 mm paper squares were discarded. Of the remaining two, one [25] showed that 3 mm cubes, for a period of 150 min, essentially shared with a rich meal the time course of gastric emptying. The other one [41] reported that spheres clearly lagged behind food, but the diameter was ~ 3.85 rather than 3 mm (Supplementary File, Table SII). Finally, it was reported that 3 mm cubes emptied more slowly than a test meal [9], but, as based on a publication from the same group, unrelated to gastric phase III of the migrating motor complex [42] (Table 1, lines 4, 13; Table II, lines 25, 26).

Table I. Temporal relationship of gastric emptying of solid meals and indigestible particles (single size)

#	Particles studied	Outcomes	Source
	Healthy subjects, indirect comparison of particle and food emptying		
1	Pellets, 0.6 – 1.2 mm	Fast pellet emptying, no effect of type of meal, median values of gastric transit time ranging from ~ 0.7 to ~ 4.5 h (read from their figure 1).	[44]
2	Ring-shaped capsules, 1 mm in thickness and 2.0, 4.5, or 7.0 mm in diameter	Very similar time courses of gastric emptying: with the 2.0, 4.5, and 7.0 mm sizes, 10/20 markers had left the stomach after 97.5, 125.3, and 100.0 min, respectively. Corresponding lag times (time to first marker leaving the stomach) were 52.5, 67.5, and 52.5 min.	[46]
3	Tablets, 7, 11, and 13 mm in diameter	Mean gastric emptying times for the 7, 11, and 13 mm tablets were 116, 128, and 171 min. Bolus emptying (all 13 mm experiments) and emptying times > 2 h (tablet size, frequency: 7 mm, 2/5; 11 mm, 3/5; 13 mm, 4/5) were taken to indicate emptying in the interdigestive period.	[31]
4	Tablets, 3, 4, 5, 6, 7 mm in diameter	The type of breakfast (light, medium, heavy) had a marked effect on 50 % emptying; there was no effect of size. With 3-5 mm sizes, mean lag times were < 60 min (light breakfast) and ≤ 80 min (heavy breakfast). Respective gastric half-emptying times were 66-114 and 155-212 min, with rather lower values in the 5-7 mm experiments (medium breakfast).	[47, 57]
5	Tubes; outer diameter, 2 mm; length, 2/10 mm	Both types of tube left the stomach together, with and without a meal. The authors considered that most markers emptied in the interdigestive phase.	[33]
6	Floating and non-floating delivery systems, diameter of at least 4.8, 7.5, and 9.9 mm (swelling over time)	Units were either floating on the gastric content or sinking down; on the average, non-floating units emptied size-dependently, with gastric residency times of 87-213 min (upright position) or 113-195 min (supine position). The authors mooted an individually variable cut-off size for emptying from the fed stomach, sometimes much higher than 2-5 mm.	[29, 51]
	Healthy subjects, direct comparison of particle and food emptying		
7	Cubes, 3 mm	Cubes and meal showed superimposed time courses of gastric emptying for 150 min (evident from figure).	[25]
8	Pieces of tubing, 2 x 5 mm	Gastric emptying of indigestible solids and digestible solids occurred simultaneously, with a light temporal advantage of the food at 120 min (87 versus 73 %, read from their figure 2).	[40]
9	Pancreatin microspheres, 2 mm diameter	Pancake emptied faster than but overlapping with the 2 mm spheres (opposite to findings in patients).	[39]
10	Tablets, 5 x 7 mm	4/8 Subjects emptied all 5 labelled tablets in the fed state, 2/8 did so with 4/5 tablets, 2 emptied only one or none of the tablets in the fed state. Conclusion: 5x7-mm tablets can empty prior to the onset of interdigestive activity.	[30]
11	Particles, diameters of 0.8-1.1 mm	Pellet exit from the stomach occurred at similar rates as the meal in 2/8 subjects, but was delayed in 6/8, in one of them extremely.	[43]
12	Tubes; outer diameter, 2 mm; length, 10 mm	50 % of the tubes had left the stomach at ~ 200 min, the value for the food label was ~ 160 min (read from their figure 7). The authors considered that most markers left the stomach in the interdigestive phase.	[32]
13	Spheres of 30 mm^3 (diameter ~ 3.85 mm)	Food clearly emptied faster than the spheres.	[41]
14	Cylinders, 2 x 5 mm	Cylinders and meal emptied together, indistinguishable for the first 90 or 120 min (read from their figure 1), later with some delay of the particles.	[27]
15	Pancreatin microspheres, 2 mm diameter	Gastric microsphere emptying started two hours after ingestion of the liquid test meal.	[36]
	Patients with pancreatic disease		
16	Pancreatin microspheres, diameter 2 mm	2 mm Spheres emptied faster than a pancake meal (opposite to finding in healthy subjects).	[39]
17	Pancreatin granules, 1.0-1.5 mm	Granules and liver pate emptied simultaneously.	[52]
18	Pancreatin pellets, diameter < 1.2 mm	Food emptied faster in 6, pellets in 5 patients; about equal rates were measured in 1 patient.	[53]

Line numbers correspond to Table SII of the Supplemental Material

There is no guarantee that much smaller particulates show more reliable emptying, as radiolabelled pellets as small as 0.8–1.1 mm diameter emptied at rates similar to food in just 2 of 8 volunteers, but later than food in the remaining six subjects. In one of the latter cases, pellet exit was delayed until the contractions associated with phase 2 and phase 3 of the interdigestive migrating motor complex [43]. A sizable diversity even of low size pellets is also evident from a report on numerous volunteer groups (6-8 individuals each) [44] (Table II, lines 1 and 11). Pellets of 0.6-1.2 mm diameters obviously passed the pylorus in the fed state but mean gastric transit times (defined by the time for half of the tracer to leave the stomach) filled the entire time range staked out by Tougas et al. [45] for a low-fat meal.

Temporal relationship with food emptying, direct comparisons of different sizes in healthy persons

Direct comparison between particles of different sizes should be especially instructive (Supplementary File, Table SIII). Of twelve such studies, performed in healthy subjects taking a solid meal (Supplementary File, Table SIII), three [23, 46, 47] found that all particles left the stomach within the fed state, with no advantage of smaller particles within a size range of 1 to 7 mm. Another study found no difference between 2x2 mm tubes and 2x10 mm tubes and concluded that particles left the stomach in the interdigestive phase (Table I, lines 2, 4, 5, and Table II, line 22) [33].

In three further studies, a particle diameter of 3.0 or 3.6 mm seemed to restrict gastric emptying to the interdigestive phase [48, 49, 50] (Table II, lines 19, 23, 24). However, in cube studies, only minor differences between 1.5 and 3 mm sizes were obtained [26, 42] (Table II, lines 25 and 26). The authors emphasized that all cubes emptied before the onset of gastric phase III motor activity; 7 mm cylindric particles behaved similarly but emptied more slowly [42].

Size effects were observed in studies listed in Table I (lines 3 and 6). For one, a size effect was observed in experiments with floating and non-floating delivery devices, sized at least 4.8-9.9 mm [29]. Gastric emptying times suggested to the authors in an antecedent letter [51] that the cut-off size enabling transpyloric passage in the digestive phase can sometimes be much higher than 2-5 mm. This is supported by the results of Khosla and Davis [31]. Respective mean gastric emptying times of tablets with diameters of 7, 11, and 13 mm were 116, 128, and 171

Table II. Size dependence of gastric emptying of indigestible particles of different sizes, taken with a solid meal

#	Particles studied	Outcomes	Reference
		Healthy subjects	
19	Caffeine (0.7 mm diameter) and acetaminophen (3.6 mm diameter) tablets	0.7 mm pellets were emptied faster than 3.6 mm pellets with both types of meal, appearance of the latter coinciding with phase II fasted state activity.	[48]
20	Pancreatin micropellets, 1-1.2 and 1.8-2 mm diameters	Faster accumulation of exhaled ^{14}C for the smaller size micropellets in 3 of 10 patients, with less obvious differences in the remaining patients (no statistical significance)	[354]
21	Spheres, 1, 1.6, 2.4 and 3.2 mm in diameter	- 1.0 mm Spheres emptied faster than 2.4 and 3.2 mm spheres. - 50 % retention times (mean of all tests) of 1.0, 1.6, 2.4, and 3.2 mm spheres were 101, 152, 203, and 152 min, respectively; that of chicken liver was 134 min. - No difference between higher- and lower-calorie meals. - Compared to chicken liver, 1.6 mm spheres emptied in parallel in 2/4 volunteers, much faster in one and much slower in the last one. - Extrapolation, based on emptying data of all sphere sizes, suggested that 1.4 mm spheres would have emptied at the same rate as chicken liver (cf. Fig. 3).	[28]
22	Pancreatin microspheres, 1 and 2 mm in diameter	Dose-dependent emptying of spheres, no significant effect of sphere size on gastric emptying, both kinds of sphere lagging behind oil in the first hour (comparison with previous data from the same laboratory).	[23]
		Patients with pancreatic disease	
23	Tablets, 3 and 10 mm in diameter	In nearly all instances, tablets emptied after the food had emptied completely. The authors suggested that the sphincter pylori had opened to allow tablet emptying.	[49]
24	Caffeine (0.7 mm diameter) and acetaminophen (3.6 mm diameter) tablets	0.7 mm pellets were emptied faster than 3.6 mm pellets, appearance of the latter coinciding with phase II fasted state activity.	[50]
25	3 mm Cubes; 1.5 and 3 mm cubes in a condition-finding experiment	Both kinds of cube emptied more slowly than food, 3 mm cubes being slightly slower; the respective retained gastric contents for food,1.5 and 3,0 mm cubes (%-%-%, min) were: 60-90-90, 60; 28-72-61, 120; 7-54-49, 180; all read from their figure 1).	[26]
26	Cubes of 1.5 or 3.0 mm side lengths; cylindrical particles of a 7 mm diameter (height not given)	All 1.5 and 3.0 mm cubes emptied within 4.5 h, the smaller ones with a slight tendency to exit more rapidly. There was no evidence of antral phase III activity before all cubes had been emptied from the stomach. Exit of the 7 mm particles was slower, but at least a portion (30 %) emptied within 1 hour.	[42]
27	Pancreatin microspheres, 1.2 and 2.0 mm diameters	~40 % of the oil had left the stomach within 60 min but only < 15 % of either type of sphere. From 150-300 min, pancreatin (both preparations) and oil emptying was synchronous.	[22]

Line numbers correspond to Table SIII of the Supplemental Material

min. Bolus emptying was observed in all experiments with 13 mm, but only in some cases with the smaller-sized tablets. The incidence of emptying times >2 hours was 2/5, 3/5, and 4/5 for the three sizes, respectively. In two cases, 7 mm tablets left the stomach within <60 min. The authors concluded that even 11 mm particles may leave the stomach in the fed state, whereas a diameter of 13 mm marks a threshold.

Finally, Meyer et al. [28] (Table II, line 21) reported a size effect within diameters ranging from 1 to 3.2 mm (1 mm significantly different from 2.4 and 3.2 mm). Spheres with 1.6 mm diameter emptied together with chicken liver in 2 of 4 volunteers, but much faster or much more slowly in the remaining two subjects. This widely cited study is the only one to report an inverse relation between transpyloric passage and diameters within a range of lower sizes (1–3.2 mm). It will receive more attention further below.

Temporal relationship with food emptying in pancreatic disease

Unfortunately, results in pancreatic patients are hardly more elucidating than those in healthy volunteers (Table I, lines 16-18; Table 2, lines 27, 34). Strikingly, 2 mm pellets left the stomach even faster in patients with chronic pancreatitis than a pancake meal did [39], a finding that carries some weight since the reverse order was obtained in the same study for volunteers. However, parallel emptying of liver pate and 1.5 mm pellets (range 1-1.5 mm) was found in patients with the same condition [52] and pylorus passage of spheres with 1.2 and 2 mm diameters alike was found to trail that of the ingested oil in patients with cystic fibrosis [22]. Finally, also in cystic fibrosis patients, diverging behaviours of <1.2 mm pancreatin pellets compared to a pancake meal [53] were reported: parallel gastric emptying in only 1 patient, faster in 5 and slower in 6 patients. A liquid meal study, in which faster emptying of smaller spheres (1-1.2 versus 1.8-2 mm) was observed in 3 of 10 patients [35] (Table II, line 20), is addressed below.

The quest for the optimal particle size

Studies seminal to the 1.4/2 mm threshold hypothesis

For the most part, the notion of a 1.4-or 2.0-mm threshold for pylorus passage of indigestible particles rests on two studies: one in patients with PEI [35] and, with a higher impact, one in volunteers [28].

Kühnelt et al. [35] (Table II, line 20) used the cholesterol-^{14}C-octanoate breath test to compare lipolytic efficacy of microspheres sized 1-1.2 mm and 1.8-2 mm in patients with PEI. Three of ten patients presented a much earlier increase in lipolytic activity with the smaller-size spheres. As the remaining patients revealed "less obvious" differences only, the overall effect was limited and not statistically significant. However, the test meal was mostly liquid, which is not representative of solid meals for reasons discussed above.

In an orientating series on gastric emptying, various sphere sizes (0.5–2.4 mm) were titrated against radiolabelled chicken liver to find out which diameter would come closest to the food emptying time [28] (Table II, line 21). Of the 9 subjects examined, 4 received spheres of 1.6 mm, 4 were tested at lower sizes, and 1 at a larger size. Based on these 9 experiments, it was estimated, without further elaboration, that spheres of 1.4±0.3 mm would empty as fast as the chicken liver. Of these experiments, only those on 1.6 mm spheres are reported in detail. It is striking that the emptying curves of liver and spheres run closely together in two subjects, whereas one subject showed much faster emptying of the spheres (more than 80% within 60 min, associated with less than 80 % emptying of the liver), and the last subject retained more than 90 % of the spheres at 150 min when already 60 % of the liver had left the stomach.

The main experiments in this study featured direct comparisons of emptying rates of 1 and 2.4 mm diameter spheres (two test meals of different caloric contents), of 1 and 3.2 mm diameter spheres (lighter meal), of 1.6 mm spheres of different densities (larger meal), and, finally, of 2.4 mm spheres and chicken liver (both meal types). Combining all these data yielded very similar curves when 15% and 50% emptying times and area under the emptying time courses were plotted against sphere size. In the 50% emptying plot, the respective mean values for the chicken liver emptying projected on the curve at about 1.4 mm, coinciding with the value reported for the orientating experiment [28]. Even so, the large heterogeneity of the results makes it difficult to deduce a fixed threshold from these experiments, also because the value of 1.4 mm rests on extrapolation rather than actual measurements. However, the published illustrations, presented without error bars and with an abridged y axis, seem to have been persuasive enough to make the 1.4 mm (or, more often, a 2 mm) limit a perceived absolute threshold for transpyloric passage in the fed state, more so than a conventional presentation with error bars and a conventional ordinate (Fig. 3) might have been. Of note, such a far-reaching interpretation is at odds with the authors´ conclusion that microspheres should average ca. 1.4 mm to consistently match the emptying rate of ^{99m}Tc-labeled chicken liver.

Clinical relevance of sphere size

The ultimate test for the medical relevance of mechanistic considerations is the outcome of clinical trials. In a more recent Cochrane review [54], comparisons of different preparations of enteric-coated microspheres revealed no statistically significant difference among the PP for any of the measured outcomes

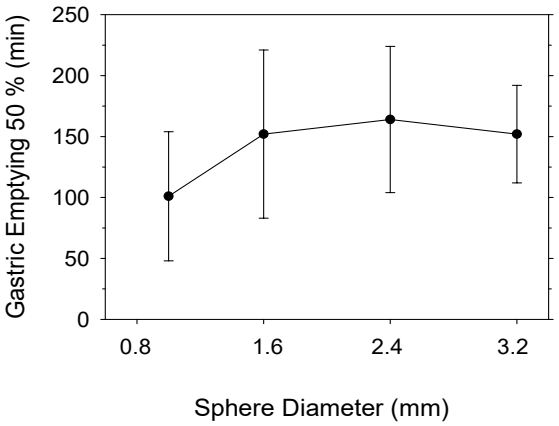

Fig. 3. Gastric emptying of indigestible spheres as a function of diameter, according to data from [28]; as opposed to the published figure, this illustration shows the error bars (SD, same publication) and uses a conventional (unshortened) y axis.

in cystic fibrosis patients. Unfortunately, there is a paucity of similar studies in pancreatic disease unrelated to cystic fibrosis. However, also a comparison between such microspheres and so-called enteric-coated mini-microspheres (pellet sizes of ≤1.6 mm) identified no statistically significant difference in the efficacy in the setting of chronic pancreatitis [55].

Particle size in guidelines

Surprisingly, relevant European guidelines provide no detailed rationale for their recommendation that pancreatin substitution be based on pellets with ≤2 mm diameters. The German guideline [5] cites two studies [28, 56] for the notion that clinical efficacy of PP, among other factors, is determined by the size of the pancreatin particles. Neither publication supports this point: one was conducted in healthy volunteers [28] and the other one [56], performed in patients with severe PEI, found no difference in clinical efficacy between 2 mm microtablets and capsules filled with 1-2 mm spheres.

The European guideline [6] states that mini-microspheres of 1–1.2 mm in diameter are associated with higher therapeutic efficacy compared to 1.8-2 mm microspheres. This is erroneously referred to a study of Bruno et al. [39], who neither compared pellets of different sizes nor studied therapeutic efficacy

Thus, the guideline-sanctioned limits are based on fragile evidence and are not supported by the available data, gathered in healthy volunteers or in patients diagnosed with PEI.

DISCUSSION

Size-dependent transpyloric transport

The threshold of <2 mm as the required diameter for adequate mixture of PP with chyme is a claim that originates from an interpretation of the findings offered by Meyer et al. [28], who concluded that "…microspheres should average ca. 1.4 mm to consistently match the emptying rate of…chicken liver ", which by no means suggests that spheres of diameters >1.4 (or 2) mm are retained in the fed stomach. Furthermore, chicken liver is not representative of all types of food, as admitted by Meyer et al. in the years to follow (e.g., [22,23]).

Indeed, it has been known for at least 20-30 years that particles as large as 5-7 mm (or even larger) can leave the stomach in the fed state [30, 47, 57, 58]. Our comprehensive analysis lays solid ground to the early perception of a gradation of sizes, over which emptying becomes both slower and more variable as particle size increases, rather than an abrupt cut-off value [57]. While particles up to a certain size, perhaps 3 mm, may freely pass the pylorus [37], larger ones will increasingly often pass in more than one step, carried into the antrum and trapped there in a first propulsive wave before they will finally be squeezed through the pylorus by a subsequent contraction [30, 31, 47, 57, 58].

In a remarkable study, Coupe et al. [30] found, on average, that 60% (3/5) of 5x7 mm tablets left the stomach within 98 min (mean of 8 subjects), which is much faster than the 1.6 mm spheres used by Meyer et al. [28] in three different experiments. The mean 50% emptying times of ~120 min (n=4), >210 min (n=6), and ~200 min (all read from figures) may also reflect different meal compositions (scrambled eggs on toast versus steak and chicken liver), which would underscore that extrapolation between different kinds of meals is unwarranted.

Sphere size limit for food-aligned transpyloric permeation

The central question is about a size limit for pancreatin spheres to be respected for a synchronous duodenal delivery with nutrients. That such a limit cannot be precise is most obvious for fatty meals. According to Trang et al. [59], the asynchrony of dietary fat and microbead emptying in the first postprandial hour, during which the fat is leaving the spheres behind and thus escapes (pancreatic) digestion in the duodenum, is the major reason of steatorrhea not adequately controlled by PP. On the other hand, spheres may even empty prior to the meal [39]. Minimizing temporal dissociation of fat and sphere emptying by an optimized timing of drug administration [59] would therefore be a reasonable but still challenging remedy.

Fig. 4 provides a compact illustration of the outcome of the present exercise. It becomes obvious that there is no fixed size limit at 2 mm, not to mention 1.4 mm, for particles to leave the stomach in close coordination with food. Rather, there is a gradation of sizes, over which gastric emptying becomes slower and more variable as particle size increases. Even 7 mm (or 11 mm) particles may be emptied from the fed stomach. The absence of an easy rule is perhaps best exemplified by the observation that the exit of 2 mm tubings and 3-mm cubes may be synchronized with that of food, while, on the other hand, particles of less than 2 mm may be delayed until the interdigestive phase.

Strategies to synchronize gastric emptying of PP-spheres and food

The dilemma of dissociated pyloric passage of food and pancreatin spheres has inspired different recommendations. Meyer et al. [23], prompted by their observation of oil outpacing microspheres in the first postcibal hour irrespective of pellet size, advocated a combination of coated and uncoated lipases, with the latter emptying faster and in part escaping degradation by gastric acid.

Taylor et al. [53], who found faster, slower, or similar rates of food compared to sphere emptying, recommended that patients should spread their pancreatin dosage throughout the meal and pondered that patients with high dosage requirements could benefit from changing the pattern of their pancreatin supplementation. While not explicitly stated by the authors, such modifications could also involve drug intake after the meal, which would avoid too fast a delivery to the duodenum, ahead of food. Such a behaviour is suggested by findings in patients [39] and consistent with outcomes of a mixed 13C-triglyceride breath test in a randomized, three-way crossover study, also in patients, in which CO2 recovery was larger when capsules were taken with or just after meals, compared to administration just before meals [61]. Supporting a pragmatic trial-and-error approach, children with cystic fibrosis might benefit from switching the administration mode – before and after the meal - on an individual level [62].

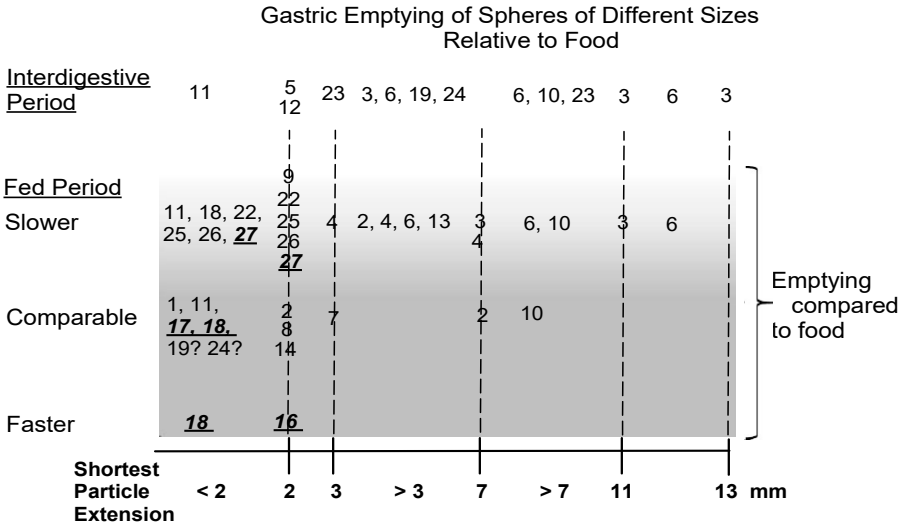

Fig. 4. Overview of the relationship between the emptying of food and particles of different sizes. Numbers refer to line numbers in Tables S1 and S2 of the Supplemental Material, denoting the various studies analysed. Shading is used to signify that slower emptying than food can mean slight as well as marked differences. The graphical arrangement of the numbers is not meant to signify quantitative differences within the various categories (Interdigestive Period, Slower, Comparable, Faster). Bold underlined numbers in italics indicate studies in patients with pancreatic disease, while the remaining studies were performed in healthy persons. Some studies investigated more than one particle size and hence appear more than once. Asymmetrical particles such as 2x5 mm tubing were categorized by their shortest extension, as they were found to pass the pylorus in longitudinal alignment. In two cases (#19, #24) question marks denote the fact that categorization as "comparable" is plausible, but not deducible by the methods used in those studies.

Strengths and limitations of this study

While previous reviews [59, 60] have critically discussed the existence of a fixed size limit for optimal emptying of PP from the stomach during meal intake, there has been no systematic review of the relevant database. The systematic approach is the strength of the present review, together with a more in-depth analysis of the core data.

Limitations of the present study are mostly related to the modest quality of the available database. In most cases, gastric emptying has been investigated in small groups of healthy volunteers. However, it has not been investigated in patients with pancreatic disease, which is accompanied with a range of other functional changes not limited to gastric emptying. Furthermore, the majority of treatment studies with PP have been performed in the setting of cystic fibrosis, which limits extrapolation to PEI in chronic pancreatitis of different etiologies. It is only recently that the need for studies filling knowledge gaps regarding effects of sphere size, shape, differences in coating and other factors has been emphasized [59]. This list may be extended by studies in patients with causes of PEI other than cystic fibrosis.

Figure S1 of the Supplemental Material illustrates how, in the light of the present review, the cycle of gastric motor activity conforms to emptying of particles of different sizes.

CONCLUSIONS

This systematic review provides evidence that the claim of strict thresholds of indigestible particles (diameters of 1.4 or 2 mm) for pyloric passage is not supported by sufficient experimental evidence. On the contrary, emptying of PP with a particle size up to 7 mm, although with some temporal delay, is documented in the postprandial phase. This information is important as it will be relevant in the selection of PP for the individual patient.

The therapeutic needs of individual patients will vary with age, pathogenesis and severity of disease, individual disposition in terms of anatomical or postsurgical settings, composition of meals, and even from day to day. Thus, it is impossible to serve the needs of all patients with one and the same PP. Rather than chasing the magic bullet, it may be appropriate to support patients in finding the best administration schedule and the individually most effective PP in the range of marketed PP (Supplementary file, Table SIV).

Conflicts of interest: In the course of the past two years, K.U.P. has received consulting fees from BioQPharma, Hexal, Nordmark, PAION, and VarmX; P.M. has received consulting fees: Bayer, Danone, Mayoly-Spindler, Nordmark, and lecturing fees from Alfa-Sigma, Bayer, Malesci, Mayoly-Spindler, and Takeda; J.M. has received consulting fees from Nordmark and lecture fees from Falk-Foundation.

Authors' contribution: K.U.P. designed and performed the literature search; K.U.P., P.M., and A.M. screened the identified articles for relevance to the topic and agreed on selection and interpretation; K.U.P. wrote the article, with contributions from P.M. and A.M.; each author critically read and edited the entire article. All authors have approved the final version of the submitted article, including the authorship list.

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REFERENCES

1. Kalser MH, Leite CA, Warren WD. Fat assimilation after massive distal pancreatectomy. N Engl J Med 1968;279:570-576. doi:10.1056/NEJM196809122791103
2. Regan PT, Malagelada JR, Dimagno EP, Go VL. Reduced intraluminal bile acid concentrations and fat maldigestion in pancreatic insufficiency: correction by treatment. Gastroenterology 1979;77:285-289.
3. Fieker A, Philpott J, Armand M. Enzyme replacement therapy for pancreatic insufficiency: present and future. Clin Exp Gastroenterol 2011;4:55-73. doi:10.2147/CEG.S17634
4. Löhr JM, Hummel FM, Pirilis KT, Steinkamp G, Körner A, Henniges F. Properties of different pancreatin preparations used in pancreatic exocrine insufficiency. Eur J Gastroenterol Hepatol 2009;21:1024-1031. doi:10.1097/MEG.0b013e328328f414
5. Hoffmeister A, Mayerle J, Beglinger C, et al. English language version of the S3-consensus guidelines on chronic pancreatitis: Definition, aetiology, diagnostic examinations, medical, endoscopic and surgical management of chronic pancreatitis. Z Gastroenterol 2012;53:1447-1495. doi:10.1055/s-0041-107379
6. Löhr JM, Dominguez-Muñoz E, Rosendahl J, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United European Gastroenterol J 2017;5:153-199. doi:10.1177/2050640616684695
7. Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097. doi:10.1371/journal.pmed.1000097
8. Bertrand J, Metman EH, Dorval ED, et al. Gastric evacuation time following a standard meal as determined by radio-opaque granules. Clinical applications and validation (author's transl). Gastroenterol Clin Biol 1980;4:770- 776.
9. Stotzer PO, Fjälling M, Grétarsdóttir J, Abrahamsson H. Assessment of gastric emptying: comparison of solid scintigraphic emptying and emptying of radiopaque markers in patients and healthy subjects. Dig Dis Sci 1999;44:729-734. doi:10.1023/a:1026609808495
10. Loreno M, Bucceri AM, Catalano F, Blasi A, Brogna A. Gastric clearance of radiopaque markers in the evaluation of gastric emptying rate. Scand J Gastroenterol 2004;39:1215-1218. doi:10.1080/00365520410003560
11. Meyer JH, Elashoff J, Porter-Fink V, Dressman J, Amidon GL. Human postprandial gastric emptying of 1-3-millimeter spheres. Gastroenterology 1988;94:1315-1325. doi:10.1016/0016-5085(88)90669-5
12. Timmermans J, Moes AJ. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy. J Pharm Sci 1994;83:18-24. doi:10.1002/jps.2600830106
13. Akkermans LMA, Houghton LA, Brown NJ. Neural and hormonal control of pyloric sphincter function. Scand J Gastroenterol 1989;24(suppl 171):27-31. doi:10.3109/00365528909091369
14. Ramkumar D, Schulze KS. The pylorus. Neurogastroenterol Motil. 2005;17 (Suppl 1):22-30. doi:10.1111/j.1365-2982.2005.00664.x
15. Chapter 11. Anatomy of the pyloric ring. In. Keet AD. The pyloric spincter in health and disease. Available at: http://med.plig.org/11/index.html. Accessed May 17, 2020.
16. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release 2000;63:235-259. doi:10.1016/s0168-3659(99)00204-7
17. Feldman M, Friedman KS, Brandt LJ. (eds). Sleisenger´s and Fordtran´s Gastrointestinal and Liver Disease. 10th ed. Philadelphia: Saunders Elsevier; 2016:816-822.
18. Soni S, Ram V, Verma A. Updates on approaches to increase the residence time of drug in the stomach for site specific delivery: Brief review. Int Curr Pharm J 2018;6:81-91. doi:10.3329/icpj.v6i11.36436
19. Kong F, Singh RP. Disintegration of solid foods in human stomach. J Food Sci 2008;73:R67-R80. doi:10.1111/j.1750-3841.2008.00766.x
20. Marciani L, Gowland PA, Spiller RC, et al. Effect of meal viscosity and nutrients on satiety, intragastric dilution, and emptying assessed by MRI. Am J Physiol Gastrointest Liver Physiol 2001;280:G1227-G1233. doi:10.1152/ajpgi.2001.280.6.G1227
21. Söderlind E, Dressman JB. Physiological factors affecting drug release and absorption in the gastrointestinal tract. In: Dressman JB, Reppas C. (eds). Oral drug absorption, prediction and assessment. 2nd ed. New York – London: Informa Healthcare; 2010:1-20.
22. Camilleri M, Malagelada JR, Brown ML, Becker G, Zinsmeister AR. Relation between antral motility and gastric emptying of solids and liquids in humans. Am J Physiol 1985;249:G580-G585. doi:10.1152/ajpgi.1985.249.5.G580
23. Calbet JA, MacLean DA. Role of caloric content on gastric emptying in humans. J Physiol 1997;498:553-559. doi:10.1113/jphysiol.1997.sp021881
24. Mazzawi T, Bartsch E, Benammi S, et al. Gastric emptying of low- and high-caloric liquid meals measured using ultrasonography in healthy volunteers. Ultrasound Int Open 2019;5:E27-E33. doi:10.1055/a-0783-2170
25. Okabe T, Terashima H, Sakamoto A. Determinants of liquid gastric emptying: comparisons between milk and isocalorically adjusted clear fluids. Br J Anaesth 2015;114:77-82. doi:10.1093/bja/aeu338
26. Velchik MG, Reynolds JC, Alavi A. The effect of meal energy content on gastric emptying. J Nucl Med 1989;30:1106-1110.
27. Weiner K, Graham LS, Reedy T, Elashoff J, Meyer JH. Simultaneous gastric emptying of two solid foods. Gastroenterology 1981;81:257-266.
28. Meyer JH, Lake R. Mismatch of duodenal deliveries of dietary fat and pancreatin from enterically coated microspheres. Pancreas 1997;15:226-235. doi:10.1097/00006676-199710000-00003
29. Meyer JH, Lake R, Elashoff JD. Postcibal gastric emptying of pancreatin pellets: effects of dose and meal oil. Dig Dis Sci 2001;46:1846-1852. doi:10.1023/a:1010666510755
30. Coupe AJ, Davis SS, Evans DF, Wilding IR. Correlation of the gastric emptying of non-disintegrating tablets with gastrointestinal motility. Pharm Res 1991;8:1281-1285. doi:10.1023/a:1015855829864
31. Khosla R, Davis SS. The effect of tablet size on the gastric emptying of non-disintegrating tablets. Int J Pharm 1990;62:R9-R11. doi:10.1016/0378-5173(90)90243-W
32. Feldman M, Smith HJ, Simon TR. Gastric emptying of solid radiopaque markers: studies in healthy subjects and diabetic patients. Gastroenterology 1984;87:895-902.
33. Smith HJ, Feldman M. Influence of food and marker length on gastric emptying of indigestible radiopaque markers in healthy humans. Gastroenterology 1986;91:1452-1425. doi:10.1016/0016-5085(86)90200-3

34. Clarke GM, Newton JM, Short MD. Gastrointestinal transit of pellets of differing size and density. Int J Pharm 1993;100:81-92. doi:10.1016/0378-5173(93)90078-T
35. Kühnelt P, Mundlos S, Adler G. The size of enteric-coated microspheres influences the intraduodenal lipolytic activity. Z Gastroenterol 1991;29: 417-421.
36. Mundlos S, Kühnelt P, Adler G. Monitoring enzyme replacement treatment in exocrine pancreatic insufficiency using the cholesteryl octanoate breath test. Gut. 1990;31:1324-1328. doi:10.1136/gut.31.11.1324
37. Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powell DW. Textbook of Gastroenterology. 5th ed. Philadelphia: John Wiley and Sons; 2011.
38. Layer P, von der Ohe MR, Holst JJ, et al. Altered postprandial motility in chronic pancreatitis: role of malabsorption. Gastroenterology 1997;112:1624-1634. doi:10.1016/s0016-5085(97)70045-3
39. Bruno MJ, Borm JJ, Hoek FJ, et al. Gastric transit and pharmacodynamics of a two-millimeter enteric-coated pancreatin microsphere preparation in patients with chronic pancreatitis. Dig Dis Sci 1998;43:203-213. doi:10.1023/a:1018813229334
40. Brogna A, Catalano F, Mangiameli A, et al. Simultaneous measurement of gastric emptying of digestible and indigestible solids in healthy humans. Ital J Gastroenterol 1992;24:188-191.
41. Jian R, Assael T, Grall Y, et al. Comparative study of gastric emptying of digestible and nondigestible solids in normal man and duodenal ulcer patients. Gastroenterol Clin Biol 1983;7:272-276.
42. Stotzer PO, Abrahamsson H. Human postprandial gastric emptying of indigestible solids can occur unrelated to antral phase III. Neurogastroenterol Motil 2000;12:415-419. doi:10.1046/j.1365-2982.2000.00218.x
43. Coupe AJ, Davis SS, Evans DF, Wilding IR. Do pellet formulations empty from the stomach with food? Int J Pharm 1993;92:167-175. doi:10.1016/0378-5173(93)90276-L
44. Davis SS, Hardy JG, Fara JW. Transit of pharmaceutical dosage forms through the small intestine. Gut 1986;27:886-892. doi:10.1136/gut.27.8.886
45. Tougas G, Eaker EY, Abell TL, et al. Assessment of gastric emptying using a low fat meal: establishment of international control values. Am J Gastroenterol 2000;95:1456-1462.
46. Horikawa Y. Gastric emptying of three different size of indigestible radiopaque markers in healthy subjects. J Smooth Muscle Res 1998;34:83-88. doi:10.1540/jsmr.34.83
47. Khosla R, Feely LC, Davis SS. Gastrointestinal transit of non-disintegrating tablets in fed subjects. Int J Pharm 1989;53:107-117. doi:10.1016/0378-5173(89)90234-2
48. Choe SY, Neudeck BL, Welage LS, Amidon GE, Barnett JL, Amidon GL. Novel method to assess gastric emptying in humans: the Pellet Gastric EmptyingTest. Eur J Pharm Sci 2001;14:347-353. doi:10.1016/s0928-0987(01)00196-8
49. Podczeck F, Mitchell CL, Newton JM, Evans D, Short MB. 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 2007;59:1527-1536. doi:10.1211/jpp.59.11.0010
50. Rhie JK, Hayashi Y, Welage LS, et al. Drug marker absorption in relation to pellet size, gastric motility and viscous meals in humans. Pharm Res 1998;15:233-238. doi:10.1023/a:1011962501270
51. Timmermans J, Moes AJ. The cutoff size for gastric emptying of dosage forms. J Pharm Sci 1993;82:854. doi:10.1002/jps.2600820821
52. Norregaard P, Lysgaard Madsen J, Larsen S, Worning H. Gastric emptying of pancreatin granules and dietary lipids in pancreatic insufficiency. Aliment Pharmacol Ther 1996;10:427–432. doi:10.1111/j.0953-0673.1996.00427.x
53. Taylor CJ, Hillel PG, Ghosal S, et al. Gastric emptying and intestinal transit of pancreatic enzyme supplements in cystic fibrosis. Arch Dis Child 1999;80:149-152. doi:10.1136/adc.80.2.149
54. Somaraju UR, Solis-Moya A. Pancreatic enzyme replacement therapy for people with cystic fibrosis. Cochrane Database Syst Rev 2016;11:CD008227. doi:10.1002/14651858.CD008227.pub3
55. Halm U, Löser C, Löhr M, Katschinski M, Mössner J. A double-blind, randomized, multicentre, crossover study to prove equivalence of pancreatin minimicrospheres versus microspheres in exocrine pancreatic insufficiency. Aliment Pharmacol Ther 1999;13: 951-957. doi:10.1046/j.1365-2036.1999.00566.x
56. Lankisch PG, Lembcke B, Kirchhoff S, Hilgers R, Creutzfeldt W. Therapy of pancreatogenic steatorrhea. Comparison of 2 acid-protected enzyme preparations. Dtsch Med Wochenschr 1988;113:15-17. doi:10.1055/s-2008-1067584
57. Khosla R. Gastrointestinal transit of dosage forms (dissertation). Nottingham, UK: U of Nottingham; 1987. Available at:http://eprints.nottingham.ac.uk/12741/1/378958.pdf. Accessed May 17, 2020.
58. Banker S, Rhodes CT, eds. Modern Pharmaceutics. 4th ed. New York – Basel: Marcel Dekker; 2002.
59. Trang T, Chan J, Graham DY. Pancreatic enzyme replacement therapy for pancreatic exocrine insufficiency in the 21st century. World J Gastroenterol 2014;20:11467-11485. doi:10.3748/wjg.v20.i33.11467
60. Newton JM. Gastric emptying of multi-particulate dosage forms. Int J Pharm 2010;395:2-8. doi:10.1016/j.ijpharm.2010.04.047
61. Domínguez-Muñoz JE, Iglesias-García J, Iglesias-Rey M, Figueiras A, Vilariño-Insua M. Effect of the administration schedule on the therapeutic efficacy of oral pancreatic enzyme supplements in patients with exocrine pancreatic insufficiency: a randomized, three-way crossover study. Aliment Pharmacol Ther 2005;21:993-1000. doi:10.1111/j.1365-2036.2005.02390.x
62. van der Haak N, Boase J, Davidson G, et al. Preliminary report of the ^{13}C-mixed triglyceride breath test to assess timing of pancreatic enzyme replacement therapy in children with cystic fibrosis. J Cyst Fibros 2016;15:669-674. doi:10.1016/j.jcf.2016.03.008