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

Karl-Uwe Petersen1, Peter Malfertheiner2, Joachim Mössner3

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].

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.
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.](image-url)
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].

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, Lorenzo 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 I, 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 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 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 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 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 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 similar rates.
### Table I. Temporal relationship of gastric emptying of solid meals and indigestible particles (single size)

<table>
<thead>
<tr>
<th>#</th>
<th>Particles studied</th>
<th>Outcomes</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pellets, 0.6 – 1.2 mm</td>
<td>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).</td>
<td>[44]</td>
</tr>
<tr>
<td>2</td>
<td>Ring-shaped capsules, 1 mm in thickness and 2.0, 4.5, or 7.0 mm in diameter</td>
<td>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.</td>
<td>[46]</td>
</tr>
<tr>
<td>3</td>
<td>Tablets, 7, 11, and 13 mm in diameter</td>
<td>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 &gt; 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.</td>
<td>[31]</td>
</tr>
<tr>
<td>4</td>
<td>Tablets, 3, 4, 5, 6, 7 mm in diameter</td>
<td>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 &lt; 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).</td>
<td>[47, 57]</td>
</tr>
<tr>
<td>5</td>
<td>Tubes; outer diameter, 2 mm; length, 2/10 mm</td>
<td>Both types of tube left the stomach together, with and without a meal. The authors considered that most markers emptied in the interdigestive phase.</td>
<td>[33]</td>
</tr>
<tr>
<td>6</td>
<td>Floating and non-floating delivery systems, diameter of at least 4.8, 7.5, and 9.9 mm (swelling over time)</td>
<td>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.</td>
<td>[29, 51]</td>
</tr>
<tr>
<td>7</td>
<td>Cubes, 3 mm</td>
<td>Cubes and meal showed superimposed time courses of gastric emptying for 150 min (evident from figure).</td>
<td>[25]</td>
</tr>
<tr>
<td>8</td>
<td>Pieces of tubing, 2 x 5 mm</td>
<td>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).</td>
<td>[40]</td>
</tr>
<tr>
<td>9</td>
<td>Pancreatin microspheres, 2 mm diameter</td>
<td>Pancake emptied faster than but overlapping with the 2 mm spheres (opposite to findings in patients).</td>
<td>[39]</td>
</tr>
<tr>
<td>10</td>
<td>Tablets, 5 x 7 mm</td>
<td>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.</td>
<td>[30]</td>
</tr>
<tr>
<td>11</td>
<td>Particles, diameters of 0.8-1.1 mm</td>
<td>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.</td>
<td>[43]</td>
</tr>
<tr>
<td>12</td>
<td>Tubes; outer diameter, 2 mm; length, 10 mm</td>
<td>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.</td>
<td>[32]</td>
</tr>
<tr>
<td>13</td>
<td>Spheres of 30 mm³ (diameter ~ 3.85 mm)</td>
<td>Food clearly emptied faster than the spheres.</td>
<td>[41]</td>
</tr>
<tr>
<td>14</td>
<td>Cylinders, 2 x 5 mm</td>
<td>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.</td>
<td>[27]</td>
</tr>
<tr>
<td>15</td>
<td>Pancreatin microspheres, 2 mm diameter</td>
<td>Gastric microsphere emptying started two hours after ingestion of the liquid test meal.</td>
<td>[36]</td>
</tr>
</tbody>
</table>

### 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. | [32]         |
| 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 min.

<p>| Table II. Size dependence of gastric emptying of indigestible particles of different sizes, taken with a solid meal |
|---|---|---|</p>
<table>
<thead>
<tr>
<th>#</th>
<th>Particles studied</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Caffeine (0.7 mm diameter) and acetaminophen (3.6 mm diameter) tablets</td>
<td>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.</td>
</tr>
<tr>
<td>20</td>
<td>Pancreatin micropellets, 1-1.2 and 1.8-2 mm diameters</td>
<td>Faster accumulation of exhaled 14C for the smaller size micropellets in 3 of 10 patients, with less obvious differences in the remaining patients (no statistical significance)</td>
</tr>
<tr>
<td>21</td>
<td>Spheres, 1, 1.6, 2.4 and 3.2 mm in diameter</td>
<td>- 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).</td>
</tr>
<tr>
<td>22</td>
<td>Pancreatin microspheres, 1 and 2 mm in diameter</td>
<td>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).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>Tablets, 3 and 10 mm in diameter</td>
<td>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.</td>
</tr>
<tr>
<td>24</td>
<td>Caffeine (0.7 mm diameter) and acetaminophen (3.6 mm diameter) tablets</td>
<td>0.7 mm pellets were emptied faster than 3.6 mm pellets, appearance of the latter coinciding with phase II fasted state activity.</td>
</tr>
<tr>
<td>25</td>
<td>3 mm Cubes; 1.5 and 3 mm cubes in a condition-finding experiment</td>
<td>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.</td>
</tr>
<tr>
<td>26</td>
<td>Cubes of 1.5 or 3.0 mm side lengths; cylindrical particles of a 7 mm diameter (height not given)</td>
<td>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.</td>
</tr>
<tr>
<td>27</td>
<td>Pancreatin microspheres, 1.2 and 2.0 mm diameters</td>
<td>~40 % of the oil had left the stomach within 60 min but only &lt; 15 % of either type of sphere. From 150–300 min, pancreatin (both preparations) and oil emptying was synchronous.</td>
</tr>
</tbody>
</table>

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 II, 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 pancreatic 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-14C-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 99mTc-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.
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. 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].
Pancreatin products - relevance of sphere size

Experimental evidence. On the contrary, emptying of PP with or 2 mm) for pyloric passage is not supported by sufficient
of strict thresholds of indigestible particles (diameters of 1.4
conforms to emptying of particles of different sizes.

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.

Acknowledgements: This work was supported by an unconditional
grant of Nordmark (Uetersen, Germany).

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
REFERENCES


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


