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Floating Microsphere Technology Mechanistic Insight and Recent Advances: A Review

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ABSTRACT

Scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems modified-shape systems, high-density systems, and other delayed gastric emptying devices. The various buoyant preparations include hollow microspheres (microballons), granules, powders, capsules, tablets (pills), and laminated films. Most of the floating systems reported in literature are single-unit systems, such as the HBS(Hydrodynamically balanced systems) and floating tablets.

Key words: Gastric residence time; Gastric emptying time; hydrodynamically balanced systems; Microballoons; Gastroretentive systems

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INTRODUCTION

Oral controlled drug delivery system (DDS) should be primarily aimed at achieving more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localize the DDS within desired regions of the gastrointestinal (GI) tract and the highly variable nature of gastric emptying process. It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 h. This variability, in turn, may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine.[1] More than 50% of drug delivery systems available in the market are oral drug delivery systems. These systems have the obvious advantages of ease of administration

and patient acceptance. One would always like to have ideal drug delivery systems that will possess two main properties: (1) it will be a single dose for the whole duration of treatment, and (2) it will deliver the active drug directly at the site of action. Unfortunately, such ideal systems are not available. Thus, scientists try to develop systems that can be as close to an ideal system as possible. There are certain situations in which gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems. Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric-retention system. Certain types of drugs can benefit from using gastroretentive devices. These include drugs that act locally in the stomach, are primarily absorbed in the stomach; are poorly soluble at an alkaline pH, have a narrow window of absorption, and degrade in the colon.[2] The relatively brief GET in humans, which normally averages 2–3 h through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the DDS leading to diminished efficacy of the administered dose. Thus, control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drugs exhibiting an absorption window in the GI tract or drugs with a stability problem. Overall, the intimate contact of the DDS with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption.[3&4]

Various methods have been applied- γ-scintigraphy, radiology(X-rays),endoscopy, ultrasonography, radiotelemetry and magnetic marker monitoring in order to study the parameters affecting the process of gastric emptying.[5&6] The most important parameters affecting gastric emptying and gastric retention time of oral dosage forms include: 1.Density,size and shape of the device[7&8] 2.Concomitant ingestion of food and its nature, caloric content and frequencyof intake[8,9&10]

3.Simultaneous administration of drugs with impact on gastrointestional transit time; for examples ,drugs acting as anticholinergic agents(e.g. atropine, propantheline), opiates(e.g. codeine) and prokinetic agents (metoclopramide, cisapride [11] 4.Biological factors such as gender, posture, age, sleep, body mass index, physical activity and disease states (e.g. diabetes, Crohn`s disease.[12,13&14].

Gastric emptying is well recognized that the stomach may be used as a `depot' for sustained-release (SR) dosage forms, both in human and veterinary applications. The stomach is anatomically divided into three parts: fundus, body, and antrum (or pylorus). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying [15]

The process of gastric emptying occurs both during fasting and fed states; however, the pattern of motility differs markedly in the two states. In the fasted state, it is characterized by an interdigestive series of electrical events which cycle both through the stomach and small intestine every 2–3 h [16.] This activity is called the interdigestive myoelectric cycle or migrating myoelectric complex (MMC), which is often divided into four consecutive phases. As described by Wilson and Washington [17], phase I is a quiescent period lasting from 40 to 60 min with rare contractions.

Phase II is a period of similar duration consisting of intermittent action potentials and contractions that gradually increase in intensity and frequency as the phase progresses. Phase III is a short period of intense, large regular contractions lasting from 4 to 6 min. It is this phase, which gives the cycle the term `housekeeper' wave, since it serves to sweep undigested materials out of the stomach and down the small intestine. As phase III of one cycle reaches the end of the small intestine, phase III of the next cycle begins in the duodenum. Phase IV is a brief transitional phase that occurs between phase III and phase I of two consecutive cycles. In the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed [18.] In other words, feeding results in a lag time prior to the onset of gastric emptying.

Scintigraphic studies involving measurements of gastric emptying rates in healthy human subjects have revealed that an orally administered CR dosage form is mainly subject to two physiological adversities: the short GRT and the variable (unpredictable) GET. Yet another major adversity encountered through the oral route is the first-pass effect, which leads to reduced systemic bioavailability of a large number of drugs. Overall, the relatively brief GI transit time of most drug products, which is approximately 8–12 h, impedes the formulation of a once daily dosage form for most drugs. These problems can be exacerbated by alterations in gastric emptying that occur due to factors such as age, race, sex, and disease states, as they may seriously affect the release of a drug from the DDS. It is, therefore, desirable to have a CR product that exhibits an extended GI residence and a drug release profile independent of patient related variables.

various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floating systems [19], swelling and expanding systems [20-21], bioadhesive systems [22,23-24], modified-shape systems [25-30], high-density systems [31-33], and other delayed gastric emptying devices [34-35]. FDDS or hydrodynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in plasma drug concentrations in some cases. Swelling type dosage forms are such that after swallowing, these products swell to an extent that prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred to as `plug type systems' since they exhibit a tendency to remain lodged at the pyloric sphincter. Bioadhesive systems are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner [22]. The approach involves the use of bioadhesive polymers that can adhere to the epithelial surface of the GI tract. The proposed mechanism of bioadhesion is the formation of hydrogen- and electrostatic bonding at the mucus-polymer boundary [17]. Rapid hydration in contact with the muco-epithelial surface appears to favor adhesion, particularly if water can be excluded at the reactive surfaces 1. Modified-shape systems are nondisintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modulus of the drug delivery device [25-30]. High-density formulations include coated pellets, which have a density greater than that of the stomach contents (~1.004 g/cm^3). This is accomplished by coating the drug with a heavy inert material such as barium sulfate, zinc oxide, titanium dioxide, iron powder, etc. Other delayed gastric emptying approaches of interest include sham feeding of indigestible polymers [36-38] or fatty acid

salts [34,35,39] that change the motility pattern of the stomach to a fed state, thereby decreasing the gastric emptying rate and permitting considerable prolongation of drug release.

Gastric Retention Advantages

1. Sustained drug delivery

As mentioned earlier, drug absorption from oral CR dosage forms is often limited by the short GRT available for absorption. However, HBS type dosage forms can remain in the stomach for several hours and, therefore, significantly prolong the GRT of numerous drugs . These special dosage forms are light, relatively large in size and do not easily pass through the pylorus, which has an opening of approximately 0.9–1.9 cm [29] It is worth noting here that a prolonged GRT is not responsible for the slow absorption of a lipophilic drug such as isradipine that has been achieved with a `floating' modified-release capsule[40]. This is because the major portion of drug release from the modified-release capsule took place in the colon, rather than in the stomach. However, the assumed prolongation in the GRT is postulated to cause sustained drug-release behavior [41]

A recent study by a Chinese group indicated that the administration of diltiazem floating tablets twice a day may be more effective compared to normal tablets in controlling the blood pressure of hypertensive patients [42] Although there was no significant difference between the two formulations in terms of maximal decreases in systolic and diastolic pressure, the duration of hypotensive effects was longer with floating tablets than that with normal ones. Further, the $t_{1/2}$ (6.4±4.4 h) and C_{max} (56±23 ng/ml) were longer and lower for floating tablets than those of normal tablets (2.3±1.1 h and 96±30 ng/ml, $P<0.01$), respectively; however, the two formulations were bioequivalent.

In case of Madopar® HBS, the formulation has been shown to release levodopa for up to 8 h in vitro, whereas the release from the standard Madopar® formulation is essentially complete in less than 30 min [43] Pharmacokinetic (PK) studies in Parkinsonian patients and healthy volunteers have also revealed that Madopar® HBS behaves as a controlled/slow-release formulation of L-dopa and benserazide [44-45] In comparison with standard Madopar®, the rate of absorption was reduced, providing lower peak concentrations of L-dopa. Further, the drug was released and absorbed over a period of 4–5 h, thus maintaining substantial plasma concentrations for 6–8 h after dosing [44]

Desai and Bolton [18]compared the dissolution profiles of floating theophylline CR tablet (300 mg) and a commercial SR tablet (Theo-Dur®; 300 mg). They found that floating tablets showed a more gradual release of the drug. The initial release rate was found to be comparatively faster, with a slower rate after 8 h. On the other hand, the release rate of Theo-Dur® was slower initially but increased later. However, these differences were not statistically significant, and two formulations were regarded as bioequivalent.

2. Site-specific drug delivery

A floating dosage form is a feasible approach especially for drugs such as furosemide and riboflavin, which have limited absorption sites in the upper small intestine. In fact, the absorption of furosemide has been found to be site-specific, the stomach being the major site of absorption, followed by the duodenum [47] This property prompted the development of a monolithic floating dosage form for furosemide, which could prolong the GRT, and thus its bioavailability was increased [48] Recently, a bilayer floating capsule has been used to achieve local delivery of

misoprostol at the gastric mucosa level [49] It is a synthetic prostaglandin E_1 analog approved and marketed in the US (as Cytotec®) for prevention of gastric ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs). Basically it replenishes the GI-protective prostaglandins that are depleted by NSAIDs. Thus, the controlled, slow delivery of misoprostol to the stomach provides sufficient local therapeutic levels and limit the systemic and intestinal exposure to the drug. This reduces the side effects that are caused by the presence of the drug in the blood circulation (uterotonic activity), or a combination of intestinal and systemic exposure (diarrhea), while maintaining its antiulcer efficacy. In addition, the prolonged gastric availability of the misoprostol from a site-directed delivery system may also reduce the dosing frequency [50] Floating tablets containing 20–50 mg of 5-fluorouracil have been successfully evaluated in four patients with stomach neoplasms in which tablets remained floating in the stomach for a period of 2 h after administration [51]

3. Pharmacokinetic advantages and future potential

As sustained release systems, floating dosage forms offer various potential advantages evident from several recent publications. Drugs that have poor bioavailability because their absorption is restricted to the upper GI tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailabilities. For instance, a significant increase in the absolute bioavailability of the floating dosage form of furosemide has been obtained (42.9%), compared to the commercially available tablet (Lasix®; 33.4%) and enteric product (Lasix® long; 29.5%) . Furthermore, among these three dosage forms, only the floating dosage form yielded satisfactory in vitro results that were significantly correlated ($P<0.05$) with in vivo absorption kinetics. The findings of this study were based on a previous postulation that site-specific absorption and longer GRT could possibly increase the bioavailability of furosemide [47] Similar observations were made by Ichikawa et al. [52] who found that floating pills containing *p*-aminobenzoic acid, a drug with a limited absorption site in the GI tract, had 1.61 times greater AUC than the control pills (32.29±6.06 vs. 20.10±5.81 μg·h/ml). These authors, however, did not find any significant difference in bioavailabilty of isosorbide-5-nitrate when floating and control pills were compared. This difference in results could be explained by the fact that isosorbide-5-nitrate is well absorbed from both the stomach and small intestine. Thus, prolonging the GRT of a dosage form appears to offer no advantage (in terms of bioavailability) for drugs with multiple absorption sites in the GI tract [s1]

Pharmacokinetic studies by Miyazaki et al. [53] demonstrated that floating granules of indomethacin prepared with chitosan were superior to the conventional commercial capsules in terms of the decrease in the peak plasma concentration and maintenance of indomethacin concentration in plasma. The values of various bioavailability parameters are shown in . There are only few instances in which the relative bioavailability of a floating dosage form is reduced compared to the conventional dosage form. An illustrative example is that of SR floating tablets of amoxycillin trihydrate the in vivo evaluation of which in healthy fasted males indicated that the relative bioavailability was reduced to 80.5% when compared with the conventional capsules; other pharmacokinetic parameters indicated no improved efficacy even though the tablets remained buoyant for 6 h and had a satisfactory release pattern in vitro [54] However, the lower bioavailability of drugs could be balanced in part by potential clinical advantages of FDDS, and may be compensated by taking a higher daily dose. For instance, in patients with advanced Parkinson's disease, who experienced pronounced fluctuations in symptoms while on standard L-dopa

treatment, a HBS dosage form provided a better control of motor fluctuations [55-56] (for review, see Ref. [57], although its bioavailability had been found to be 50 to 60% of the standard formulation [45,58]. There were significant improvements with regard to both akinetic and dyskinetic phenomena.

The reduced fluctuations in the plasma levels of drugs result from delayed gastric emptying. After oral dosing the bioavailability of standard Madopar® has been found to be 60–70%; the difference in bioavailabilities of standard and HBS formulations seems to be due to incomplete absorption rather than an altered disposition of the drug [44]. Cook et al. [59] demonstrated that a HBS capsule containing iron salts has an increased efficacy and reduced side effects. Floating dosage forms with SR characteristics can also be expected to reduce the variability in transit performance [60] and various pharmacokinetic parameters [45]. It might be expected that developing HBS dosage form for tacrine might provide a better delivery system and reduce its GI side effects in Alzeihmer's patients. In addition, buoyant delivery systems might provide a beneficial strategy for the treatment of gastric and duodenal cancers.

The concept of FDDS has also been utilized in the development of various anti-reflux formulations. Washington et al. [61] investigated the gastric distribution and residence time of a pectin-containing formulation. They observed that the formulation was able to float and form a discrete phase on top of the stomach contents. Indeed, the product emptied from the stomach more slowly than the food ($P<0.05$), and more than 50% of the formulation remained in the fundal region for 3 h. Atyabi et al. [62] reported a floating system prepared from anionic exchange resins that could also be used as a protective barrier (`floating seal') against gastroesophageal reflux. Todd and Fryers [63] have described a similar pharmaceutical composition that could be used in the treatment of biliary gastritis, which results from duodeno-gastric reflux of bile into the stomach. Apart from aforementioned advantages, floating systems are particularly useful for acid-soluble drugs [17], drugs which are poorly soluble or unstable in intestinal fluids [64], and those which may undergo abrupt changes in their pH-dependent solubility due to factors such as food, age and pathophysiological conditions of the GI tract.

Developing controlled release systems for such drugs as bromocriptine might lead to potential treatment of Parkinson's disease. After oral administration, approximately 30% of the dose is absorbed from the GI tract [65]. However, its low absorption potential, which often results from low dose usage, might be improved by a HBS dosage form, which could significantly enhance its therapeutic efficacy. Furthermore, the co-delivery of bromocriptine and metoclopramide based on a dual delivery concept similar to that of the Madopar® HBS might further improve the therapeutic efficacy of the HBS dosage form. The use of metoclopramide, a standard antiemetic agent, is justifiable since it can prevent the side effects caused especially by high doses of bromocriptine [66].

Another therapeutic area in which FDDS can be explored is the eradication of *Helicobacter pylori*, which is now believed to be the causative bacterium for chronic gastritis and peptic ulcers. Although the bacterium is highly sensitive to most antibiotics, its eradication from patients requires high concentrations of drug be maintained within the gastric mucosa for a long duration [67]. Recently Katayama et al. [68] developed a SR liquid preparation of ampicillin using sodium alginate that spreads out and adheres to the gastric mucosal surface whereby the drug is

continuously released. Thus, it can be expected that topical delivery of a narrow-spectrum antibiotic through a FDDS may result in complete removal of the organisms in the fundal area of the gastric mucosa due to bactericidal drug levels being reached in this area, and might lead to better treatment of peptic ulcer disease.

Factors influencing gastric retention time

There are several factors that can affect gastric emptying (and hence GRT) of an oral dosage form. These factors include density, size, and shape of dosage form, concomitant intake of food and drugs such as anticholinergic agents (e.g., atropine, propantheline), opiates (e.g., codeine) and prokinetic agents (e.g., metoclopramide, cisapride), and biological factors such as gender, posture, age, body mass index, and disease states (e.g., diabetes, Crohn's disease). Most of these factors have been described here in the context of FDDS.

FDDS are retained in the stomach for a prolonged period of time by virtue of their floating properties, which can be acquired by several means. Generally speaking, in order for a HBS dosage form to float in the stomach, the density of the dosage form should be less than the gastric contents. A density of less than 1.0 g/ml has been reported in the literature. However, the floating force kinetics of such dosage forms has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyant capabilities. The buoyant capabilities are better represented and monitored by resultant-weight measurements and swelling experiments [69]. This is because the magnitude of floating strength may vary as a function of time and usually decreases after immersion of the dosage form into the fluid as a result of the development of its hydrodynamic equilibrium [70].

One of the earlier in vivo evaluations of FDDS by Müller-Lissner et al. [71] demonstrated that a GRT of 4–10 h could be achieved after a fat and protein test meal. Furthermore, food affects the GRT of dosage forms depending on its nature, caloric content and the frequency of intake [48,72,73]. For example, Oth et al. [48] reported that the mean GRT of a bilayer floating capsule of misoprostol was 199±69 min after a single light meal (breakfast). However, after a succession of meals, the data showed a remarkable prolongation of the mean GRT, to 618±208 min. In another study, Iannuccelli et al. [74] reported that in the fed state after a single meal, all the floating units had a floating time (FT) of about 5 h and a GRT prolonged by about 2 h over the control. However, after a succession of meals, most of the floating units showed a FT of about 6 h and a GRT prolonged by about 9 h over the control, though a certain variability of the data owing to mixing with heavy solid food ingested after the dosing was observed. Obviously, when the gastroretentive properties of a floating dosage form is independent of meal size, it can be suggested that the dosage form will be suitable for patients with a wide range of eating habits [75].Interestingly, most of the studies related to effects of food on GRT of FDDS share a common viewpoint that food intake is the main determinant of gastric emptying, while specific gravity has only a minor effect on the emptying process [33,40,76,77]. Stated otherwise, the presence of food, rather than buoyancy, is the most important factor affecting GRT and floating does not invariably increase GRT. In fact, studies have shown that the GET for both floating (F) and non-floating (NF) single units are shorter in fasted subjects (less than 2 h), but are significantly prolonged after a meal (around 4 h) [33,77]. In a similar study, Agyilirah et al. [78] found that in the fed state, balloon (floating) tablets prolonged the GET by an average of 6 h over that of uncoated, nondisintegrating tablets; however, in the fasted state, the balloon tablets did not significantly prolong GET and

both tablets had much shorter emptying times compared to the fed state. Studies of Mazer et al. [40] suggested that the release and absorption kinetics of a lipophilic drug (isradipine) from a `floating' modified-release capsule might be affected by intragastric interaction with the lipid phase of a high-fat meal. Further, for the modified-release capsule, GRT was regarded as the duration of intragastric release to reach 90% release, since no further intragastric release could occur after the capsule left the stomach. Thus, in view of foregoing discussions, it may be concluded that although floating systems possess an inherent ability for gastric retention, they rely more on the presence of a meal to retard their emptying.

This consistency can be explained based on the fact that the gastric emptying depends on the onset of the MMC. Therefore, the GRT is significantly increased under fed conditions, since the onset of MMC is delayed [18]. Nevertheless, the efficiency of intragastric buoyant dosage forms in the fed stomach is questionable because of the intensive contractile activity of the stomach and the density of the viscous chyme. Moreover, in the fasted stomach the amount of liquid is not sufficient for the drug delivery buoy and the stomach's entire contents are emptied down the small intestine within 2–3 h because of the typical phase III activity [41].

Concern regarding the role of food in the prolongation of the GRT has also provided insights into other determinants of gastric retention. For instance, studies have shown that the GRT of a dosage form in the fed state can also be influenced by its size. Small-size tablets are emptied from the stomach during the digestive phase, while larger-size units are expelled during the housekeeping waves [48]. Timmermans et al. [79] studied the effect of size on the GRT of F and NF units using γ-scintigraphy. They found that F units with a diameter equal to or less than 7.5 mm had longer GRTs compared to NF units. However, the GRTs were similar for F and NF units having a larger diameter of 9.9 mm. This study also demonstrated that F units, which remain buoyant on gastric contents, are protected against gastric emptying during digestive phases. On the other hand, NF units lie in the antrum region and are propelled during the digestive process by peristalsis.

The prolongation of the GRT by food is expected to maximize drug absorption from a FDDS. This may be rationalized in terms of increased dissolution of drug and longer residence at the most favorable sites of absorption. However, there may be rare exceptions, where the presence or absence of food in the stomach has no effect on the absorption of a drug from HBS type dosage forms [44]. The effects of food on various aspects of drug absorption have been extensively discussed in a separate publication [80]. Apart from food and buoyancy effects, there are other biological factors that can influence the GRT. Sangekar et al. [76] concluded that the increase in retention time of HBS may also be due to effects such as adhesion to the gastric mucosa, rather than the effect of floating per se. Mojaverian et al. [81] investigated the effects of gender, posture, and age on the GRT of an indigestible solid, the Heidelberg capsule. As a result of this study, authors found that the mean ambulatory GRT in the males was significantly faster than in their age (±3 years)- and race-matched female counterparts (3.4±0.6 vs. 4.6±1.2 h, $P<0.01$). Further, the data indicated that women emptied their stomach slower than men, regardless of weight, height, body surface area and even when the hormonal changes due to the menstrual cycle were normalized. The mean GRT for volunteers in the supine state was not statistically significant from that in the upright, ambulatory state (3.4±0.8 vs. 3.5±0.7 h, $P>0.05$). In the case of elderly, the GRT was prolonged, especially in subjects >70 years old (mean GRT=5.8 h; $n=3$). Another confounding factor is the variability of GI transit within and between individuals. Studies by

Coupe et al. [82] revealed that variability in gastric emptying of single- and multiple-unit systems was large compared to that in small intestinal transit times; however, the intrasubject variation was less than intersubject for both gastric and small intestinal transit times.

A comparative evaluation of the gastric transit of F and NF matrix dosage forms indicated that buoyancy and non-buoyancy of the forms lead to distinct intragastric behaviors [83]. It was also concluded that depending on the subject posture, either standing or supine, the gastric residence period of a dosage form is function of either its buoyancy or the diametric size of the matrix. Recently, a triple radionuclide scintigraphic technique has been described for intragastric monitoring that allowed the measurement of the effects on GRT of galenic parameters (size, density of matrices), as well as of physiological parameters such as subject posture [84.] Studies were conducted in nonfasting human volunteers either in upright or in supine posture, who concurrently were given one optimized F and one NF hydrophilic matrix capsules of the same size, and three different sizes (small, #5; medium, #0; large, #000). In upright subjects, all the F forms stayed continuously above the gastric contents irrespective of their size, whereas the NF units sank rapidly after ingestion and never rose back to the surface thereafter. Thus, in upright subjects the F forms were protected against postprandial emptying. Consequently, the F forms showed prolonged and more reproducible GRTs compared to the NF forms. The significance and extent of this prolongation when compared with NF units were the most marked for the small size units ($P<0.001$) but gradually lessened as the dosage form size increased ($P<0.05$ for the medium size units), to become insignificant for the large size units ($P>0.05$). However, there was no significant difference between the mean GRTs of the small, medium, and large F units ($P>0.05$). These findings indirectly confirm that the intragastric buoyancy of the F forms is the main factor determining their prolonged GRTs and protecting them from random gastric emptying related to antral peristaltism [85]. Similar results were reported in a recent study [60]. The mean GRTs of the NF forms were much more variable and highly dependent on their size, which were in the order of small<medium<large units, $P<0.05$. Moreover, in supine subjects, a size effect influenced the GRT of both the F and NF forms ($P<0.05$). The F forms were more often emptied before the NF forms but size for size, the mean GRTs did not differ in the aggregate. Bennett et al. [86] have also demonstrated the role of posture in gastric emptying. They observed that an alginate raft emptied faster than food in subjects lying on their left side or on their backs and slower in subjects lying on their right side with the raft positioned in the greater curvature of the stomach. This is because when the subjects laid on their left side, the raft was presented to the pylorus ahead of the meal and so emptied faster [17].

New approaches for gastric retention time

Various approaches have been worked out to improve the retention of an oral dosage form in the stomach, eg, floating system, swelling and expanding system, bioadhesive . system, modified shape system, high-density system, and other delayed gastric-emptying devices [87,20,4,88,89,33.35]

Floating drug delivery systems (FDDS)or hydrodynamically balanced systems have a bulk density lower than gastric fluids and therefore remain floating in the stomach without affecting the gastric-emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release, the residual system is expelled from the stomach. This leads to an increase in the GRT and better control over fluctuations in plasma drug concentration. Swelling-type dosage forms are such that after swallowing, these products swell to

an extent that prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be referred to as "play-type systems" because they exhibit a tendency to remain lodged at the pyloric sphincter. Bioadhesive systems are used to localize a delivery device within the lumen cavity of the body to enhance the drug absorption process in a site-specific manner. In this approach, bioadhesive polymers are used that can adhere to the epithelial surface of the gastrointestinal tract. Mechanistically, bioadhesion involves the formation of hydrogen and electrostatic bonding at the mucus-polymer interface [90]. Modified systems are non-disintegrating geometric shapes made up of silastic elastomer or extruded from polyethylene blends, which prolong the GRT, depending on size and shape.

High-density gastro retentive systems include coated pellets that have a density greater than the stomach contents (~1.004 g/cm3). This can be achieved by coating the drug with heavy inert material, such as zinc oxide, titanium dioxide, barium sulphate, etc. Other approaches for delayed gastric emptying including use of some indigestible polymers or fatty acid salts,[35] which can change the motility of the GI tract leading to an increase in GRT and hence prolonged drug release.[35,91]

MARKETED PRODUCTS OF FLOATING DRUG DELIVERY SYSTEMS

The last three decades of intensive research work have resulted in the development of five commercial FDDS. Madopar®HBS (Prolopa®HBS) is a commercially available product used in Europe and other countries, but not available in the US. It contains 100 mg levodopa and 25 mg benserazide, a peripheral dopa decarboxylase inhibitor. This CR formulation consists of a gelatin capsule that is designed to float on the surface of the gastric fluids. After the gelatin shell dissolves, a mucus body is formed that consists of the active drugs and other substances. The drugs diffuse as successively hydrated boundary layers of the matrix dissipate [43].

Valrelease® is a second example of a floating capsule, marketed by Hoffmann-LaRoche, that contains 15 mg diazepam; the latter is more soluble at low pH. Tshus, diazepam (pK_a=3.4) absorption is more desirable in the stomach, not in the intestine where it is practically insoluble and is poorly absorbed. The HBS system maximizes the dissolution of the drug by prolonging the GRT. Moreover, pharmacokinetic data have demonstrated the blood level equivalence of once per day dosing with the HBS capsule to three times daily dosing from conventional, 5-mg Valium® tablets [92].

Floating liquid alginate preparations, e.g., Liquid Gaviscon, are used to suppress gastroesophageal reflux and alleviate the symptoms of `heart burn'. The formulation consists of a mixture of alginate, which forms a gel of alginic acid, and a carbonate or bicarbonate component (e.g., sodium bicarbonate), which reacts with gastric acid and evolve CO_2 bubbles. The gel becomes buoyant by entrapping the gas bubbles, and floats on the gastric contents as a viscous layer, which has a higher pH than the gastric contents [93].

Topalkan® is a third-generation aluminum–magnesium antacid that involves not only its antacid properties but an even greater degree the availability of alginic acid in its formula. It has antipeptic and protective effects with respect of the mucous membrane of the stomach and esophagus, and provides, together with the magnesium salts, a floating layer of the preparation in

the stomach [94]. Almagate Flot-Coat® is another novel antacid formulation that confers a higher antacid potency together with a prolonged GRT and a safe as well as extended delivery of antacid drug [95]. It is obvious that these newer formulations differ from the standard antacid products, which are either rapidly neutralized to water-soluble ions or sediment to the fundus of the stomach, and are evacuated into the duodenum by normal peristalsis [95].

Limitations of floating drug delivery system

One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach for the drug delivery buoy to float therein and to work efficiently. However, this limitation can be overcome by coating the dosage form with bioadhesive polymers, thereby enabling them to adhere to the mucous lining of the stomach wall [96]. Alternatively, the dosage form may be administered with a glass full of water (200–250 ml). Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids. Drugs such as nifedipine, which is well absorbed along the entire GI tract and which undergoes significant first-pass metabolism, may not be desirable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailablity [1]. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.

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