

# Gastroretention A Means to Address Regional Variability in Intestinal Drug Absorption

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AUTHORS

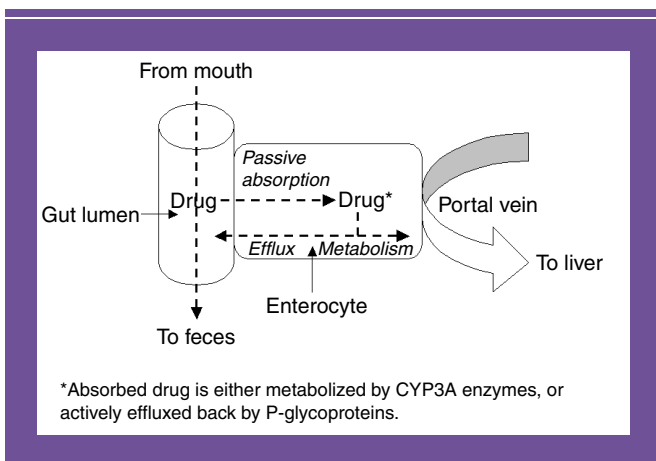
The control of gastrointestinal transit of orally administered dosage forms using gastroretentive drug delivery systems (GRDDS) can improve the bioavailability of drugs that exhibit site-specific absorption. Prolonged gastric retention can be achieved by using floating, swelling, bioadhesive, or high-density systems. This article reviews the concept of the absorption window and describes the performance evaluation of GRDDS, including in vitro–in vivo correlation studies and potential use.

Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biological parameters pertinent to their performance. Despite tremendous advancements in drug delivery, the oral route remains the preferred route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance. The extensive advancements in genomics and combinatorial chemistry have led to the synthesis of many potential drug candidates, removing the bottleneck in the drug discovery process. On the other hand, this high-throughput screening process has done little to address the issue of poor bioavailability (BA) of orally administered drug candidates.

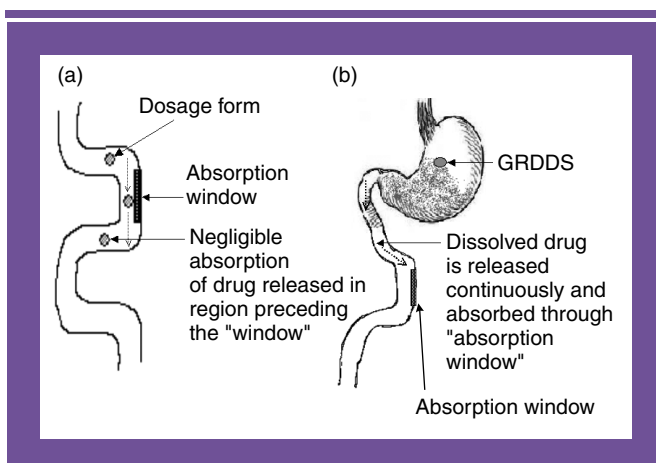
Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate (1,2). An important requisite for the successful performance of oral CRDDS is that the drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion, to ensure continuous absorption of the released drug (3). The average time required for a dosage unit to traverse the GIT is 3–4 h, although slight variations exist among various dosage forms (see Table I).

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**Figure 1:** Enteral cycling of a drug substrate for P-glycoprotein and CYP3A.



**Figure 2:** Drug absorption in the case of (a) conventional dosage forms and (b) gastroretentive drug delivery systems.

A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular portion of the GIT only or are absorbed to a different extent in various segments of the GIT (4,5). Such drugs are said to have an *absorption window*, which identifies the drug's primary region of absorption in the GIT.

An absorption window exists because of physiological, physicochemical, or biochemical factors. The pH-dependent solubility and stability level of a drug plays an important role in its absorption. A drug must be in a solubilized and stable form to successfully cross the biological membrane, and it will experience a pH range from 1 to 8 as it travels through the GIT. Because most drugs are absorbed by passive diffusion of the un-ionized form, the extent of ionization at various pH levels can lead to nonuniform absorption or an absorption window. The presence of certain enzymes in a particular region of the GIT also can lead to regional variability in the absorption of drugs that are substrates of those enzymes (6).

Perorally administered drugs are absorbed by passive diffusion processes and by nonpassive means. Drugs absorbed by active and facilitated transport mechanisms show higher regional specificity because of the prevalence of these mechanisms in only certain regions of the GIT (3). Many drugs show poor BA because of the presence of enzymes and efflux pumps. Intestinal metabolic enzymes—primarily, Phase I metabolizers such as cytochrome P450 (CYP3A)—are abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with levels rising slightly from the duodenum to the jejunum and declining in the ileum and colon. This nonuniform distribution of CYP3A causes regional variability in the absorption of drugs that are substrates of that enzyme. In addition, carriers involved in the secretion of organic molecules from the blood into the intestinal lumen may affect drug absorption (7). An example of such a secretory transporter is P-glycoprotein (P-gp), which is present in the villus tip of enterocytes and has the capacity to interact with a vast variety of drugs. P-gp sends the absorbed drug from the cytoplasm of the enterocyte back to the intestinal lumen, thus reducing the drug's BA. In the human body, these intestinal enzymes and efflux transporters work in coordination to protect against the entry of toxic agents into blood circulation.

Figure 1 depicts the mechanism involved in the interaction between drug efflux and metabolism. The enzyme metabolizes the drug molecule absorbed into the enterocyte. Then that portion of the drug is transported from the enterocyte back into the intestinal lumen by the action of P-gp, following which it is reabsorbed and again subjected to metabolism and efflux. Therefore, the drug is continually cycled between the enterocyte and the gut lumen, which allows the enzyme to have repeated access to the drug molecule, thus reducing absorption.

Drugs having site-specific absorption are difficult to design as oral CRDDS because only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption (8). After crossing the absorption window, the released drug goes to waste with negligible or no absorption (see Figure 2a). This phenomenon drastically decreases the time available for drug absorption after its release and jeopardizes the success of the delivery system.

### Gastroretentive drug delivery systems

Dosage forms that can be retained in the stomach are called *gastroretentive drug delivery systems* (GRDDS) (9). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site (10) (see Figure 2b), thus ensuring its optimal BA (11,12).

**Table 1:** Transit times of various dosage forms across the segments of the GIT.

Dosage form	Transit time (h)		
	Stomach	Small intestine	Total
Tablets	2.7 ± 1.5	3.1 ± 0.4	5.8
Pellets	1.2 ± 1.3	3.4 ± 1.0	4.6
Capsules	0.8 ± 1.2	3.2 ± 0.8	4.0
Solution	0.3 ± 0.07	4.1 ± 0.5	4.4

**Table II: Anatomical and physiological features of the human GIT.**

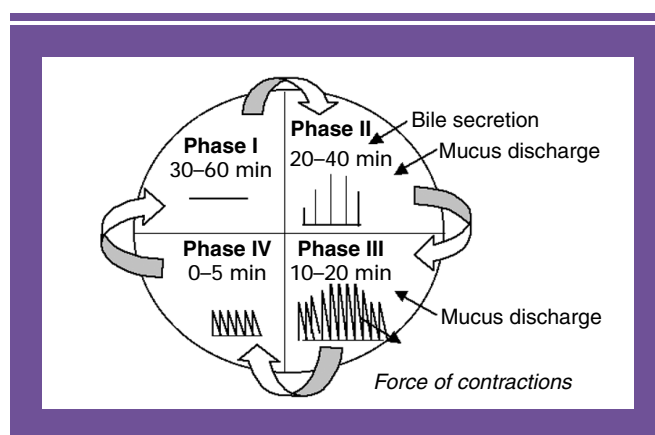
Section	Average length (cm)	Diameter (cm)	Villi present*	Absorption mechanism	pH	Major constituents	Transit time of food (h)
Oral cavity	15–20	10	–	Passive diffusion, convective transport	5.2–6.8	Amylase, maltase, ptyalin, mucins	Short
Esophagus	25	2.5	–		5–6	–	Very short
Stomach	20	15	–	Passive diffusion, convective transport	1.2–3.5	Hydrochloric acid, pepsin, rennin, lipase, intrinsic factor	0.25–3.00
Duodenum	25	5	+	Passive diffusion, convective transport, active transport, facilitated transport, ion pair, pinocytosis	4.6–6.0	Bile, trypsin, chymotrypsin, amylase, maltase, lipase, nuclease, CYP3A4	1–2
Jejunum	300	5	++	Passive diffusion, convective transport, active transport, facilitated transport	6.3–7.3	Amylase, maltase, lactase, sucrase, CYP3A5	–
Ileum	300	2.5–5.0	++	Passive diffusion, convective transport, active transport, facilitated transport, ion pair, pinocytosis	7.6	Lipase, nuclease nucleotidase, entero-kinase	1–10
Cecum	10–30	7	+	Passive diffusion, convective transport, active transport, pinocytosis	7.5–8.0	–	Short
Colon	150	5	–	Passive diffusion, convective transport	7.9–8.0	–	4–20
Rectum	15–19	2.5	–	Passive diffusion, convective transport, pinocytosis	7.5–8.0	–	Variable

\* In the “Villi present” column, “–” indicates villi are absent, “+” indicates villi are scarcely present, and “++” indicates villi are abundantly present.

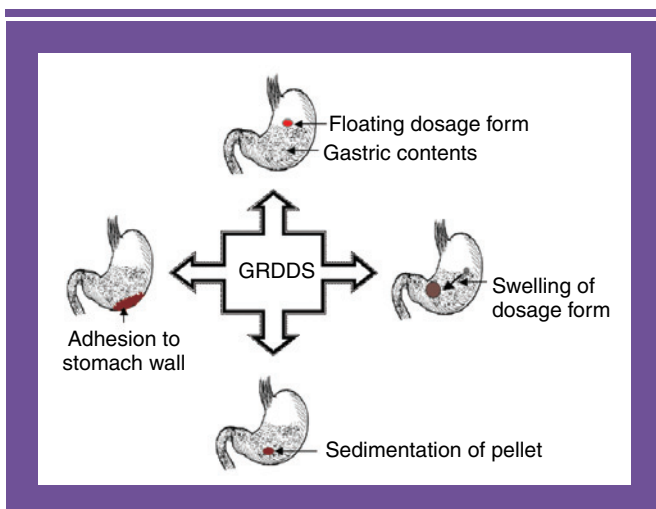
**Gastrointestinal motility patterns affecting dosage form retention.** The complex anatomy and physiology of the GIT, including variations in acidity, bile salts, enzyme content, and the mucosal absorptive surface, significantly influence the release, dissolution, and absorption of orally administered dosage forms. Table II lists the anatomical and physiological features of the GIT (13,14).

Two distinct patterns of gastrointestinal (GI) motility and secretion exist, corresponding to the fasted and fed states (15). As a result, the BA of orally administered drugs will vary depending on the state of feeding. The fasted state is associated with various cyclic events, commonly referred to as the *migrating motor complex* (MMC), which regulates GI motility patterns. The MMC is organized into alternating cycles of activity and quiescence and can be subdivided into basal (Phase I), pre-burst (Phase II), and burst (Phase III) intervals (see Figure 3).

Phase I, the quiescent period, lasts from 30 to 60 min and is characterized by a lack of secretory, electrical, and contractile activity. Phase II exhibits intermittent action for 20–40 min,



**Figure 3: Motility patterns of the GIT in the fasted state.**



**Figure 4:** Classification of gastroretentive drug delivery systems.

during which contractile motions increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of Phase II and throughout Phase III. Phase III is characterized by intense, large, and regular contractions, termed *housekeeper waves*, that sweep off undigested food and last 10–20 min. Phase IV is the transition period of 0–5 min between Phases III and I.

This series of electrical events originates in the foregut and continues to the terminal ileum in the fasted state, repeating every 2–3 h (16). Feeding sets off a continuous pattern of spike potentials and contractions called *postprandial motility*. The particular phase during which a dosage form is administered influences the performance of peroral CRDDS and GRDDS (17).

When CRDDS are administered in the fasted state, the MMC may be in any of its phases, which can significantly influence the total gastric residence time (GRT) and transit time in the GIT. This assumes even more significance for drugs that have an absorption window because it will affect the amount of time the dosage form spends in the region preceding and around the window. The less time spent in that region, the lower the degree of absorption. Therefore, the design of GRDDS should take into consideration the resistance of the dosage form to gastric emptying during Phase III of the MMC in the fasted state and

also to continuous gastric emptying through the pyloric sphincter in the fed state. This means that GRDDS must be functional quickly after administration and able to resist the onslaught of physiological events for the required period of time.

**Gastroretentive techniques.** Several techniques, including floating (11,18), swelling, inflation, and adhesion (12,19–22), have been explored to increase the gastroretention of dosage forms (see Figure 4).

**Floating systems.** Floating systems, first described by Davis in 1968, are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period (23,24). While the system floats over the gastric contents, the drug is released slowly at the desired rate (25, 26), which results in increased GRT and reduces fluctuation in plasma drug concentration (27). Floating systems can be classified as *effervescent* and *noneffervescent* systems.

**Effervescent systems.** Flotation of a drug delivery system in the stomach can be achieved by incorporating a floating chamber filled with vacuum, air, or an inert gas (28). Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the CO<sub>2</sub> produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts (29). These devices contain a hollow deformable unit that converts from a collapsed to an expanded position and returns to the collapsed position after a predetermined amount of time to permit the spontaneous ejection of the inflatable system from the stomach (21,30).

**Noneffervescent systems.** Noneffervescent systems incorporate a high level (20–75% w/w) of one or more gel-forming, highly swellable, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose [HPMC], and sodium carboxymethylcellulose), polysaccharides, or matrix-forming polymers (e.g., polycarboxophil, polyacrylates, and polystyrene) into tablets or capsules (31). Upon coming into contact with gastric fluid, these gel formers, polysaccharides, and polymers hydrate and form a colloidal gel barrier (32) that controls the rate of fluid penetration into the device and consequent drug release (19). As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density of and confers buoyancy to the dosage form.

**Bio/mucoadhesive systems.** Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The concept is based on the self-protecting mechanism of the GIT. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. Mucus is a viscoelastic, gel-like, stringy slime comprised mainly of glycoproteins. The thickness of the mucus layer de-

**Table III: Classification of bioadhesive polymers.**

Cationic	Anionic	Neutral
Polybrene	CMC	Bovine serum albumin
Poly-L-lysine	Dextran sodium	Dextran
Polylysine	Poly acrylic acid	Ficoll
Polyvinyl methyl imidazole	Poly-L-aspartic acid	Polyethylene glycol
	Polystyrene sulfonic acid	Polyethylene pyrrolidone
	Polyvinyl sulfate	
	Heparin	
	Hyaluronic acid	
	Poly glutamic acid	
	γ-Carageenan	
	Chondroitin sulfate	

creases from the membrane surface to the GI lumen. The primary function of mucus is to protect the surface mucosal cells from acid and peptidases. In addition, it serves as a lubricant for the passage of solids and as a barrier to antigens, bacteria, and viruses (14).

The epithelial adhesive properties of mucin are well known and have been applied to the development of GRDDS through the use of bio/mucoadhesive polymers (33). The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving BA (34).

A bio/mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bioadhesive polymer) or the mucus lining of the GIT (mucoadhesive polymer). The characteristics of these polymers are molecular flexibility, hydrophilic functional groups, and specific molecular weight, chain length, and conformation. Furthermore, they must be nontoxic and nonabsorbable, form noncovalent bonds with the mucin–epithelial surfaces, have quick adherence to moist surfaces, easily incorporate the drug, offer no hindrance to drug release, have a specific site of attachment, and be economical. The binding of polymers to the mucin–epithelial surface can be subdivided into three broad categories: hydration-mediated adhesion, bonding-mediated adhesion, and receptor-mediated adhesion (35).

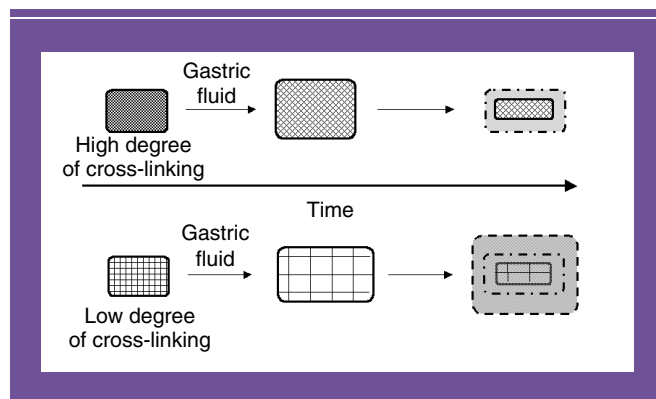
**Hydration-mediated adhesion.** Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties. The prolonged gastroretention of the bio/mucoadhesive drug delivery system is further controlled by the dissolution rate of the polymer.

**Bonding-mediated adhesion.** The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical–mechanical bonding and chemical bonding. Physical–mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., van der Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups (2).

**Receptor-mediated adhesion.** Certain polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx.

Bioadhesive polymers also can be classified on the basis of their charge. A few examples of bioadhesive polymers are listed in Table III.

An unresolved issue related to bio/mucoadhesive systems is the attachment site of the system in the gut wall. The systems can attach both to the mucus layer and the epithelial surface of the stomach. In the former case, it is important to realize that the mucus layer in the stomach turns over continuously, and the mucus can be found not only on the surface of the lumen but also within the lumen (called the *soluble mucus*) (36). Hence, it is difficult to understand how mucoadhesive systems identify the designated attachment site. In the case of bioadhesive



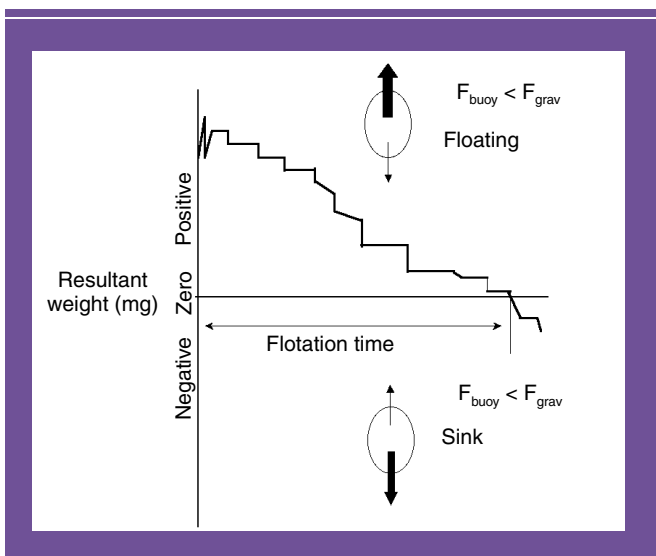
**Figure 5:** Relationship between the degree of cross-linking of the polymeric chains and the swelling behavior of swelling systems.

systems, a bioadhesion mechanism based on nonspecific interactions is unlikely to produce a demonstrable benefit in the human GIT.

**Swelling systems.** After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus (37). As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as *plug-type systems* because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state.

Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical–chemical cross-links in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system and maintains its physical integrity for a prolonged period (see Figure 5). On the other hand, a low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer (38). An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion (39). These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration (37).

**High-density systems.** These systems, which have a density of  $\sim 3 \text{ g/cm}^3$ , are retained in the rugae of the stomach (11) and are capable of withstanding its peristaltic movements (40). Above a threshold density of  $2.4\text{--}2.8 \text{ g/cm}^3$ , such systems can be retained in the lower part of the stomach (41). If this phenomenon is confirmed by clinical studies, these heavy pellet formulations may appear on the market in the near future. The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug



**Figure 6:** Effect of resultant weight during buoyancy on the floating tendency of FDDS.

(>50%) and to achieve the required density of 2.4–2.8 g/cm<sup>3</sup>. Diluents such as barium sulphate (density = 4.9), zinc oxide, titanium dioxide, and iron powder must be used to manufacture such high-density formulations.

### Evaluation of GRDDS

Any drug product must be evaluated to ensure its performance characteristics and to control batch-to-batch quality. In addition to routine tests for general appearance, hardness, friability, drug content, weight variation, uniformity of content, disintegration time, and drug release, the gastroretentive performance of GRDDS must be evaluated (42).

**Floating systems. Floating/buoyancy time.** The test for buoyancy is usually determined in 900 mL of simulated gastric (HCl/NaCl with 0.02% Tween 80, pH 1.2) or intestinal fluids (KH<sub>2</sub>PO<sub>4</sub>/NaOH buffer with 0.02% Tween 80, pH 7.4) maintained at 37 °C using the USP dissolution apparatus. These fluids simulate the surface tension of human gastric juice (35–50 mN/m<sup>2</sup>) (43). The amount of time the dosage form floats is termed the *floating time* (11). In the case of floating microparticles, the number of floating particles and the time during which they remain buoyant on the test solution can be determined (44,45). The floating process depends on the balance between the weight and volume of the dosage form. An increase in the buoyancy force caused by the increased volume causes a resultant weight increase and leads to dosage-form flotation (46).

**Specific gravity.** The specific gravity of floating systems can be determined by the displacement method, using benzene as a displacing medium (47).

**Resultant weight.** Until now, bulk density and floating duration have been the main parameters to describe the adequacy of a dosage form's buoyancy. However, although the density value may indicate whether or not an object will float, the density value does not reflect the magnitude of floating forces produced by the object (48). Moreover, a single density determination made before immersion does not predict the floating force evo-

lution of the dosage form because the dry material of which it is made progressively reacts or interacts within the gastric fluid to release its drug contents.

Therefore, an in vitro measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by measuring the force equivalent to the force *F* required to keep the object totally submerged in the fluid. This force determines the resultant weight of the object when immersed and may be used to quantify its floating or nonfloating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the vectorial sum of buoyancy (*F*<sub>buoy</sub>) and gravity (*F*<sub>grav</sub>) forces acting on the object as shown in the equation

$$F = F_{\text{buoy}} - F_{\text{grav}}$$

$$F = d_f g V - d_s g V = (d_f - d_s) g V$$

$$F = (d_f - M/V) g V$$

in which *F* is the total vertical force (resultant weight of the object), *g* is the acceleration due to gravity, *d<sub>f</sub>* is the fluid density, *d<sub>s</sub>* is the object density, *M* is the object mass, and *V* is the volume of the object (49).

By convention, a positive resultant weight signifies that the force *F* is exerted upward and that the object is able to float, whereas a negative resultant weight means that *F* acts downward and that the object sinks (see Figure 6). The crossing of the zero base line by the resultant weight curve from positive toward negative values indicates a transition of the dosage form from floating to nonfloating conditions. The intersection of lines on a time axis corresponds to the floating time of the dosage form.

**Bio/mucoadhesion systems. Bioadhesive strength.** The bioadhesive strength of a polymer can be determined by measuring the force required to separate the polymer specimen sandwiched between the layers of either an artificial (e.g., cellophane) or biological (e.g., rabbit stomach tissue) membrane (22). This force can be measured by using a modified precision balance or an automated texture analyzer.

**Swelling systems. Weight gain and water uptake (WU).** The swelling behavior of a dosage unit can be measured by studying its weight gain or WU. The study is done by immersing the dosage form in simulated gastric fluid at 37 °C and determining these factors at regular intervals. The dimensional changes can be measured in terms of the increase in tablet diameter and/or thickness over time. WU is measured in terms of percent weight gain, as given by the equation

$$WU = (W_t - W_0) \times 100/W_0$$

in which *W<sub>t</sub>* and *W<sub>0</sub>* are the weights of the dosage form at time *t* and initially, respectively (50).

Furthermore, the GRDDS should be evaluated for gastroretention and drug-release behavior.

**Gastroretention.** In vivo visualization is a crucial parameter for evaluating the GI-retention characteristics of the dosage form. The inclusion of a radio-opaque material into a solid dosage

form enables it to be visualized by X-rays. Similarly, the inclusion of a  $\gamma$ -emitting radionuclide in a formulation allows indirect external observation using a  $\gamma$ -camera or scintiscanner (51). The use of X-rays involves exposing a patient to an X-ray beam, thus permitting the visualization of the GI transit of the dosage form. In the case of  $\gamma$ -scintigraphy (52), the  $\gamma$ -rays emitted by the radionuclide are seen through a camera to monitor the location of the dosage form in the GIT (53).

**Dissolution/drug release.** Dissolution tests are performed using the USP dissolution apparatus (31). Samples are withdrawn periodically, with replacement, and analyzed for drug content after appropriate dilution. The major requirement for the dissolution test is to allow a dosage form to sink to the bottom of the vessel before the rotation of the paddle. In the case of floating systems, this can be accomplished by attaching a small, loose piece of nonreacting material, such as a few turns of wire helix, around the dosage form that would otherwise float. However, this method can inhibit the three-dimensional swelling process of the dosage form and consequently affect the drug release from the formulation (54).

An alternative is to fully submerge the dosage form under a ring or mesh assembly (55). However, in the case of swellable systems, drug release is highly dependent on full surface exposure, unhindered swelling, and drug solubility in water. Another modification is to position the paddle blades at the surface of the dissolution medium. This process allows the continuous depletion of the stagnant layer around the floating dosage form and maintains constant hydrodynamic conditions (56).

## Factors affecting GRDDS performance

**Formulation factors.** The shape of the dosage form is one of the factors that affect its GRT (57). Six shapes (ring, tetrahedron, cloverleaf, string, pellet, and disk) were screened in vivo for their gastric retention potential. The tetrahedrons (each leg 2 cm long) and rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 h. On the other hand, cloverleaves (2.2–3.2 cm in diameter) exhibited 40–67% retention; discs (2.5 cm diameter), 67%; string (12 cm  $\times$  2 mm  $\times$  2 mm/24 cm  $\times$  2 mm  $\times$  2 mm), 0%; and pellets (4 mm), 0% retention at 24 h.

Size also can determine how long a dosage form is retained in the stomach. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the housekeeping waves (58). Various gastric emptying times were observed for nondisintegrating tablets of different sizes (59). The longest gastric emptying time was observed for 13-mm tablets (171  $\pm$  13 min), followed by 11-mm (128  $\pm$  17 min) and 7-mm (116  $\pm$  19 min) tablets. These results are in accordance with the aperture of the resting pylorus, 12.8  $\pm$  7 mm (60), which can be taken as the critical value for GI transit of dosage forms of different sizes. In the case of floating systems, however, no statistically significant difference exists in the extent of gastric retention among dosage forms of different sizes, which confirms that intragastric buoyancy is the main determinant of prolonged residence in the stomach.

In the case of floating systems, formulation variables such as the viscosity grade of the polymers and their interactions significantly affect floating properties of the delivery system and

drug release. Low-viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high-viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity (61).

**Idiosyncratic factors.** The concomitant intake of food and drugs such as anticholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) and prokinetic agents (e.g., metoclopramide and cisapride), may affect the performance of GRDDS. The coadministration of GI motility-decreasing drugs can increase gastric emptying time. On the contrary, these drugs should be contraindicated with mucoadhesive systems because they reduce gastric secretion and induce the drying of mucus membranes (2).

Biological factors such as gender, age, posture, body mass index, and disease state (e.g., diabetes or Crohn's disease) also may affect gastroretention. For example, women and the elderly show slower gastric emptying than do men and younger subjects. Intrasubject and intersubject variations also are observed in gastric and intestinal transit times.

GRT increases in the presence of food, leading to increased drug dissolution and longer residence of the dosage form at the most favorable site of absorption. Furthermore, the nature, caloric content, and the frequency of food intake affect the GRT of the dosage form (58,62). A GRT of 4–10 h has been reported after a meal of fats and proteins (63). The presence of food in the stomach affects a floating system's ability to maintain an intragastric position distant from the gastroduodenal junction, which appears to prevent early and erratic emptying during the digestive phases. The buoyancy of floating dosage forms enables their retention for more than 6 h in the fed state (64).

Subject posture (e.g., standing or supine) also leads to variable intragastric behaviors. An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size (65). In subjects positioned upright, floating dosage forms show prolonged and more reproducible GRTs than conventional dosage forms (53). The conventional dosage forms sink to the lower part of the distal stomach where they are expelled through the pylorus by antral peristaltic waves.

In supine subjects, large dosage forms (both conventional and floating) experience prolonged retention. After the ingestion of meals, conventional dosage forms sink and are deposited toward the posterior gastric wall. This position offers no reliable protection against early and erratic emptying. The gastric retention of these dosage forms is therefore directly related to their size. On the other hand, floating forms appear to be equally likely to remain buoyant anywhere between the lesser and greater curvatures of the stomach. On moving distally, these units may be swept away by the contractile waves that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects. Therefore, patients preferably should not be dosed with a floating drug delivery system just before going to bed.

## In vitro–in vivo correlation

Traditionally, in vitro–in vivo correlation (IVIVC) has served as a means of modeling the human organism and of gaining a

better understanding of drug absorption and its dependence on in vitro release processes. However, the chief application of IVIVC is to use in vitro studies for quality-control procedures and as an alternative to in vivo bioequivalence studies. In addition, IVIVC is a beneficial tool for developing a dosage form with the desired in vivo performance with the fewest possible human trials.

IVIVC has been described in USP (66) as “the establishment of a relationship between a biological property, or a parameter derived from a biological property produced by a dosage form, and a physicochemical characteristic of the same dosage form.”

FDA, in turn, describes IVIVC as a process “to show a relationship between two parameters. Typically, a relationship is sought between in vitro dissolution rate and in vivo input rate. This initial relationship may be expanded to critical formulation parameters and in vivo input rate” (66).

Various levels of correlation can be defined from these definitions (67).

**Level A.** In a Level A correlation, a one-to-one relationship exists between the in vitro dissolution rate and the in vivo input rate. In this case, IVIVC alone is sufficient to determine the bio-pharmaceutical performance of a dosage form.

**Level B.** Level B indicates a correlation of statistical moments determined in vitro and after administration in vivo. It involves a comparison of the mean in vitro dissolution time (MDT) and either the mean in vivo residence or dissolution time.

**Level C.** In Level C, a point-to-point relationship exists between a dissolution parameter and a pharmacokinetic parameter. The relationship involves a comparison of a single-point measure of dissolution or release rate (such as MDT or time required for a 50% release) and a single-point measure of the extent of absorption in vivo (such as the area under the curve).

Because a Level A correlation is based on a full-time profile, it demonstrates the best fit between in vitro release and in vivo dosage form performance. A perfect Level A correlation can be established for drugs delivered by gastroretentive dosage forms. By enhancing the GRT of the delivery system, gastroretentive dosage forms allow the transit of drug in solution form for a prolonged period across its absorption site. Hence the in vitro dissolution studies conducted under the conditions simulating the in vivo environment can be correlated with the in vivo input rate (68). For example, furosemide is a weakly acidic drug ( $pK_a$  4.6) and is maximally absorbed by passive diffusion through the stomach and duodenum. The in vitro dissolution profile of the gastroretentive dosage form of furosemide, when studied at pH 3.0 using a flow-through cell, showed a linear relationship between percentage released in vitro and percentage absorbed in vivo (69). This perfect correlation was possible because of the sink conditions provided by the pH 3.0 buffer in the flow-through cell, and the prolonged retention of gastroretentive dosage form at the absorption site of furosemide. Hence, an important criterion for establishing a high degree of IVIVC for GRDDS is the selection of a dissolution medium that mimics the in vivo environment at the absorption site.

## Examples of GRDDS applications

GRDDS can improve the pharmacotherapy of oral formula-

tions and provide high and sustained drug concentrations along the gastric mucosa. For instance, the eradication of *Helicobacter pylori* requires the administration of various medications several times a day, which often results in poor patient compliance. More reliable therapy can be achieved by using GRDDS, through which the dose and frequency of drug administration can be reduced. In another example, floating alginate beads have been used for the sustained release of amoxicillin trihydrate for as long as 24 h (70).

## Limitations

GRDDS have great potential in improving the BA of drugs that exhibit an absorption window, but with certain limitations. One of the major disadvantages of floating systems is the requirement of high levels of fluids in the stomach for the delivery system to float and work efficiently. These systems also require the presence of food to delay their gastric emptying. In addition, there are limitations to the applicability of floating systems for drugs that have solubility or stability problems in the highly acidic gastric environment or that are irritants to the gastric mucosa. In the case of bioadhesive systems, which form electrostatic and hydrogen bonds with the mucus, the acidic environment and the thick mucus prevent bond formation at the mucus-polymer interface. The high turnover rate of mucus may further aggravate the problem (39). For swellable systems, the major limiting factor is that the system must maintain a size larger than the aperture of the resting pylorus for the required time period. Above all, any dosage form designed to stay in the stomach during the fasted state must be capable of resisting the housekeeper waves of Phase III of the MMC.

## Conclusion

GRDDS, comprised mainly of floating, bioadhesive, and swellable systems, have emerged as an efficient means of enhancing the BA and controlled delivery of drugs that exhibit an absorption window. By prolonging the gastric emptying time of the dosage form, these systems not only provide controlled release of the drug for a prolonged period, but also present the drug in an absorbable form at regions of optimal absorption. These systems achieve this by retaining the dosage form in the gastric region, from where the drug is presented at the absorption window. This ensures maximal absorption of the drug for the desired period. Designing GRDDS requires a thorough understanding of the physicochemical properties of the drug, the physiological events of the GIT, and formulation strategies. A careful consideration of the interplay of these parameters can help in designing a successful GRDDS. Growth in the understanding of the effect of GI physiology on drug delivery and the increasing sophistication of delivery technology will ensure the development of an increasing number of GRDDS to optimize delivery of drug molecules that exhibit regional variability in intestinal absorption.

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