# Gastric Retentive Drug-Delivery Systems

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**ABSTRACT:** The development of a long-term oral controlled-release dosage form has been difficult mainly because of the transit of the dosage form through the gastrointestinal (GI) tract. Several approaches to extend gastric residence time have been tried. The most commonly used systems are (1) intragastric floating systems, (2) high-density systems, (3) mucoadhesive systems, (4) magnetic systems, (5) unfoldable, extendible, or swellable systems, and (6) superporous hydrogel systems. The concept of each approach is examined, and improvements that are needed for further development are discussed. Background materials in the GI physiology that are necessary for understanding the concept and usefulness of each approach are also provided.

**KEY WORDS:** Gastric retentive device, oral drug delivery, gastric emptying, gastric retention, platform.

## I. INTRODUCTION

Oral administration is the most convenient and preferred means of drug delivery to the systemic circulation, and for this reason extensive research efforts have been directed toward the development of oral controlled-release dosage forms. Despite the significant advances that have been made in controlled-release drug-delivery systems during the last three decades, advances in oral controlled-release dosage forms have been rather limited. Drug-delivery technologies are advanced enough to design any dosage forms that can deliver drugs at a constant rate (i.e., zero-order) for extended periods of time ranging from days to years. And yet most oral controlled-release dosage forms deliver drugs for only 12 hours. Oral delivery for 24 hours is possible for some drugs, such as phenylpropanolamine[1] and nifedifine,[2] which are absorbed well throughout the GI tract. But oral administration of most drugs tends to have a short-term (≤12 h) limitation because, regardless of the duration of drug release, oral controlled-release

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dosage forms pass through the small intestine, where most drug absorption occurs, in much less than 12 hours. Thus, the real issue in the development of oral controlled-release dosage forms is how to extend the time for drug absorption from the small intestine. For example, oral dosage forms may have to stay in the stomach or somewhere in the upper small intestine until all the drug is released for desired periods of time. Designing platforms that target the upper small intestine is rather difficult, since they would have to be an adhesive-type system that selectively adheres to the jejunum or ileum surfaces. Carbohydrate-containing copolymers[3,4] and lectins[5-11] have been tried in order to target selective sites in the intestine. These approaches are highly promising and are expected to become practical once there is further understanding of the specific ligands present in the intestine. Currently, however, it is rather difficult to place oral dosage forms at selected sites in the small intestine. For this reason, most research efforts have been focused on platforms to extend gastric residence time.

As described below, several approaches have been tried by investigators throughout the world. Each has been tested by many different groups, and as a result the literature on gastric retention devices is extensive. There are good reviews on these devices,[12,13] but most of the available references have too much data, and many of them provide contradictory interpretations about the same approach. Describing all the data and results set forth in this extensive literature without proper analysis certainly would not help anyone understand the technologies involved in each of these systems. Instead, this paper discusses the conceptual basis for each gastric retention approach currently available, provides background discussion of the gastrointestinal (GI) physiology that is necessary for understanding such concepts, and suggests improvements that could help further the development of these existing technologies.

## A. Components of the Controlled-Release Dosage Forms

Controlled-release dosage forms consist of three major components: a drug, a drug-delivery module, and a platform (Table 1). The drug-delivery module is programmed to deliver a drug at a certain rate for a predetermined time period. The drug release rate is controlled by the rate controller, and the duration of drug delivery is determined by both the rate controller and the size of the drug reservoir. In many cases, the high concentration of a drug serves as an energy source. The platform is a component that maintains the drug-delivery module at a certain site in the body. For example, in transdermal drug-delivery systems, the skin adhesive is the platform. For oral controlled-release dosage forms, the platform is the component that maintains the drug-delivery module at a certain site in the GI tract. Since successful long-term oral controlled-release dosage forms would require suitable platforms, it is critically important to develop suitable platforms that allow extension of the effective lifetime of oral dosage forms by overcoming the limitations set by the GI physiology. Without suitable platforms for extending the GI transit time, oral dosage forms can not exploit the full benefit of controlled-release technologies.

**TABLE 1**
**Main Components of Controlled-Release Drug-Delivery Systems**

- Drug
- Drug-delivery module
  - *Drug-delivery portal*
  - *Rate controller for drug release*
  - *Energy source*
  - *Reservoir for drugs*
- Platform

## B. Drugs Usable in Gastric Retentive Devices

Gastric retentive devices may be highly useful for the delivery of many drugs. Table 2 lists some examples of drugs that can be best delivered using such devices. Gastric retentive devices would provide the best results for drugs that may act locally in the stomach or that may be absorbed primarily in the stomach. For many drugs that are absorbed (mainly) from the upper small intestine (i.e., drugs with absorption windows),

**TABLE 2**
**Drugs That Can Be Delivered Using Gastric Retentive Devices**

- Drugs that act locally in the stomach
  *(e.g., antacids, antibiotics for bacterially-based ulcers)*
- Drugs that are absorbed primarily in the stomach *(e.g., albuterol[16])*
- Drugs that are poorly soluble at an alkaline pH
- Drugs that have a narrow window for absorption
  *(that is, drugs that are absorbed mainly from the proximal small intestine,*
  *for example, riboflavin, levodopa, p-aminobenzoic acid[14,15])*
- Drugs that are absorbed rapidly from the GI tract *(e.g., amoxicillin[17,18])*
- Drugs that degrade in the colon *(e.g., metoprolol[19])*

controlled release in the stomach would result in improved bioavailability. Improved bioavailability is also expected for drugs that are absorbed readily upon release in the GI tract. Such drugs can be best delivered by slow release from the stomach.

Of course there are drugs that are not suitable for delivery in the stomach. Aspirin and nonsteroidal anti-inflammatory drugs are known to cause gastric lesions, and thus slow release of such drugs in the stomach may results in more gastric lesions. It goes without saying that drugs unstable in the acidic pH of the stomach cannot be used in gastric retentive devices. Furthermore, with those drugs that can be absorbed equally well throughout the intestine, such as isosorbide dinitrate, longer gastric retention may not provide any substantial benefit.[14,15]
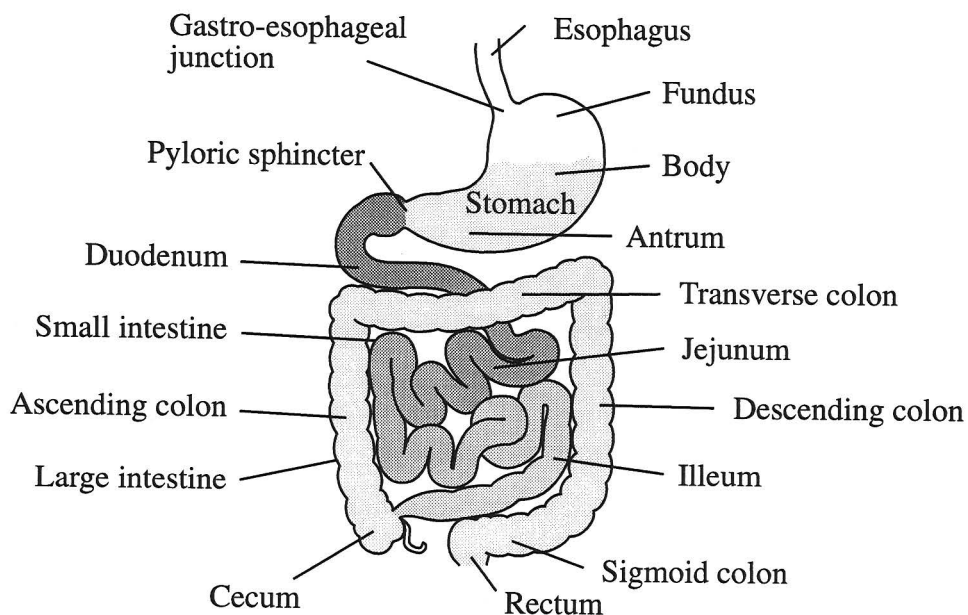


**FIGURE 1.** Schematic description of the GI tract. The absorption abilities of the different segments of the GI tract for most drugs are shown with different gray scales (the darker the region, the more absorption of the drug).

## II. UNIQUE PROPERTIES OF THE GI TRACT

Since the goal of having a proper platform is to overcome some physiological problems (e.g., gastric emptying of solid dosage forms), we will first examine some aspects of the GI tract that are relevant to drug delivery. Figure 1 shows the GI tract, which consists of the stomach, small intestine, and colon.

### A. Gastrointestinal Transit Times

One of the unique properties of the GI tract is that the food content remains in each segment of the GI tract for different time periods. Table 3 shows the residence times of both liquid and solid foods in each segment of the GI tract. The values in Table 3 should be taken as relative rather than absolute, and are intended to point out general differences among different segments in the GI tract. Since most drugs are absorbed from the upper intestine (i.e., duodenum, jejunum, and ileum) as shown in Figure 1, the total effective time for drug absorption is 3 h–8 h. This is why one has to take most drugs 3–6 times a day.

### B. Variable Absorption Abilities in the GI Tract

Another factor that makes long-term oral drug delivery more difficult is that drug transport across the intestinal epithelium in each segment is not uniform.[21] The performance of oral controlled dosage forms profoundly depends on transit through the GI tract, because the extent of drug absorption from different regions of the GI tract is different. Table 4 lists some of the features of each segment in the GI tract; as in Table 3, these values should be taken as relative. The main function of the stomach is to

## TABLE 3
### Transit Time in Each Segment of the GI Tract[20]

| Segment | Type of food | |
| --- | --- | --- |
| | Liquid | Solid |
| Stomach | 10 min–30 min | 1h–3 h |
| Duodenum | < 60 sec | < 60 sec |
| Jejunum and ileum | 3 h ± 1.5 h | 4 h ± 1.5 h |
| Colon | | 20 h–50 h |

**TABLE 4**
**Function, Morphology, and Physiology of the GI Tract[5,20]**

| Segment | Function | Size (Diameter x length) | Surface Area | pH |
|---------|----------|--------------------------|--------------|-----|
| Stomach | Digestion of foods | 15 cm x 20 cm | $3.5\ m^2$ | 1–3.5 |
| Duodenum | Neutralization of acids | 3–5 cm x 20–30 cm | $2\ m^2$ | 4–6.5 |
| Jejunum | Absorption of nutrients | 3–5 cm x 240 cm | $180\ m^2$ | 5–7 |
| Ileum | Absorption of nutrients | 3–5 cm x 360 cm | $280\ m^2$ | 6–8 |
| Colon | Absorption of water | 3–9 cm x 90–125 cm | $1.3\ m^2$ | 6–8 |

begin to digest foods and to release them through the pylorus into the duodenum. Because of the small surface area of the stomach, drug absorption from the stomach is rather minimal. The jejunum and ileum are the main sites for absorption of nutrients (drugs are in a sense nutrients). The large surface area is designed for just this purpose. In the colon, water and ions ($Na^+$ and $Cl^-$) are absorbed, but absorption of nutrients is limited. The surface area is small, but due to the potentially large residence time in the colon, drug absorption can be significant for some drugs. Unless drugs are absorbed equally as well in the colon as in the small intestine, the duration for drug absorption for most drugs is only about 3 h–8 h. The absorption abilities of most drugs decrease as they move along the intestine (i.e., the drug has a "window for absorption"), as described in Figure 1. Drugs such as nitrofurantoin, riboflavin, and allopurinol are known to be absorbed only from the upper regions of the GI tract, and these drugs require frequent administration. The change in pH values through the GI tract can also make a difference in absorption of ionizable drugs.

## C. Presystemic Clearance

Even with those drugs that can be absorbed equally well throughout the GI tract, bioavailability can still be significantly reduced by site-specific changes in presystemic clearance. Degradation of orally administered drugs can occur by hydrolysis in the stomach, enzymatic digestion in the gastric and small intestinal fluids, metabolism in the brush border of the gut wall, metabolism by microorganisms in the colon, and/or metabolism in the liver prior to entering the systemic circulation (i.e., first pass effect). Such degradation may lead to high variation or poor absorption of drug into the systemic circulation. For example, metoprolol is absorbed well from the large intestine, but presystemic clearance occurs in the large intestine.[19] This results in a decrease in drug concentration in the large intestine; as a result, the amount of absorbed drug is

decreased. As shown in Figure 2, the systemic availability of metoprolol is lower for the Oros device, which delivers the drug at a zero-order rate, compared with intragastric infusion due to the transit of Oros to the colon. Digoxin is also known to undergo microbial metabolism before absorption. For this type of drug, of which presystemic clearance is determined by the site of absorption, systemic availability is enhanced when drug delivery is restricted to the upper segment of the gut or to the stomach.[19]

The whole idea of developing a zero-order release oral dosage form was to maintain a constant drug concentration in the blood, but even such zero-order release oral dosage forms, such as the OROS system, resulted in a transient rise to a maximum and a subsequent decrease of drug concentration in the blood. For example, after oral administration in the Oros device, the plasma concentration of indomethacin reaches a peak within 4 h to approximately 600 ng/mL, and then decreases to about 100 ng/mL several hours after the peak.[22] This is mainly due to a decreasing absorption ability of the GI tract as the oral dosage form moves down the GI tract. Only in rare cases does drug concentration in the blood remain constant when delivered by a zero-order release device (e.g., delivery of phenylpropanolamine by Oros[1]). For the vast majority of drugs, oral dosage forms require a gastric retentive platform to maintain a constant blood level.
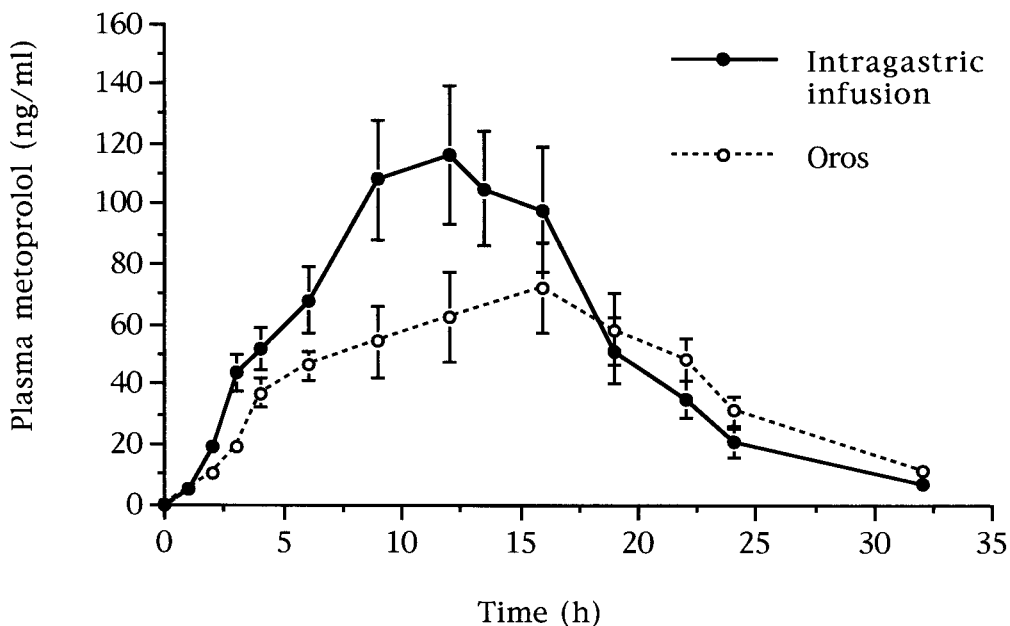


FIGURE 2. Mean plasma profiles of metoprolol after single oral dosing of metoprolol Oros (with 190 mg of metoprolol fumarate and a release rate of 14 mg/h) and intragastric infusion for 13.5 h. From Warrington, et al.[19]

## III. GASTRIC EMPTYING

The brief description of a few unique properties of the GI tract suggests that development of a long-term oral controlled-release dosage form requires an appropriate platform to overcome the limitations set by the GI tract. Extended gastric retention prolongs overall GI transit time, which will result in improved bioavailability for many drugs.[13] To develop strategies for gastric retention, one needs to know how gastric emptying occurs and what factors may control gastric emptying. Much effort has been made to identify factors affecting the GI transit of oral dosage forms. Numerous gastric-emptying studies in animals and humans have been conducted with various oral formulations. Until now, two main parameters have been identified that most influence gastric emptying of oral dosage forms: the physical properties (e.g., size and density) of the oral dosage form and the presence of food in the stomach (i.e., fasted or fed states). It is rather difficult to discuss the influences of these two factors separately, since the effect of physical properties in large part depends on the presence of food in the stomach. One of the main functions of the stomach is to digest food and deliver chyme to the intestine. Constant emptying of the gastric contents occurs as a result of gastric motor activities, which occur as a cycle. Emptying of oral dosage forms also occurs as a result of such gastric contractions. For this reason, it is important to understand how gastric emptying of oral dosage forms is related to gastric motility.

### A. Gastric Motility

Gastric emptying occurs as a result of gastric contractions, the nature of which depends on the contents of the stomach. Thus, gastric emptying can be conveniently classified into gastric emptying of liquid, digestible solids, and indigestible solids. Liquids empty from the stomach as a result of intragastric pressure generated by slow muscular contractions occurring mainly from the proximal stomach (i.e., the upper body of the stomach).[23] The removal of liquid from the stomach is first-order, i.e., the volume of liquid emptied per unit time is directly proportional to the volume remaining in the stomach. Digestible solids are known to be emptied only when they have been changed to a thick, creamy substance called chyme.[23] It is generally understood that solid particles larger than 1 mm–2 mm are retained in the stomach until they are further reduced in size,[24,25] although other reports suggest otherwise.[26,27] Peristaltic waves are contractions in the distal stomach (i.e., the lower body of the stomach) that are responsible for mixing and grinding solid food to the form required for emptying.[23] Figure 3 shows a sequence of gastric contractions removing a portion of digestible solids and liquefied food from the stomach. As the peristaltic wave approaches the distal antrum, the pylorus closes and large solid particles are retained in the stomach. Pressures of up to 60 cmH$_2$O has been measured.[23]

Indigestible solids (including oral dosage forms) are known to be emptied from the stomach in the fasting state by a distinct cycle of electromechanical activity known
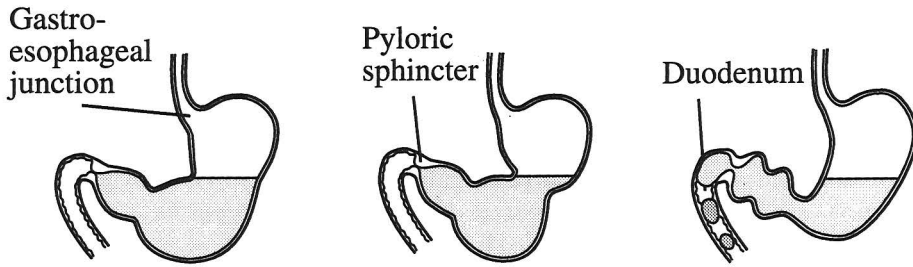
**FIGURE 3.** A sequence of gastric contractions responsible for gastric emptying of digestible solids and liquefied food from the stomach. Food is mixed with gastric juice and turned into chyme **(A)**. Peristaltic waves, which are most marked in the lower half of the stomach, move the chyme toward the still-closed pyloric sphincter **(B)**. The valve-like pyloric sphincter opens to allow only small quantities of food to pass into the duodenum at a time **(C)**. From Clayman.[28]

as the interdigestive migrating myoelectric complex (IMMC). The reported size of indigestible solids emptied in the fasted state varies from 1 mm–2 mm[29] to 7 mm.[30] Due to considerable intersubject differences, even solid particles larger than 10 mm are not guaranteed to achieve an appropriate gastric retention in every patient.[31] The IMMC is composed of four motor activities known as Phases 1–4, as shown in Figure 4. Phase 1 (basal state) is a period without any motor activity, except for rare con-
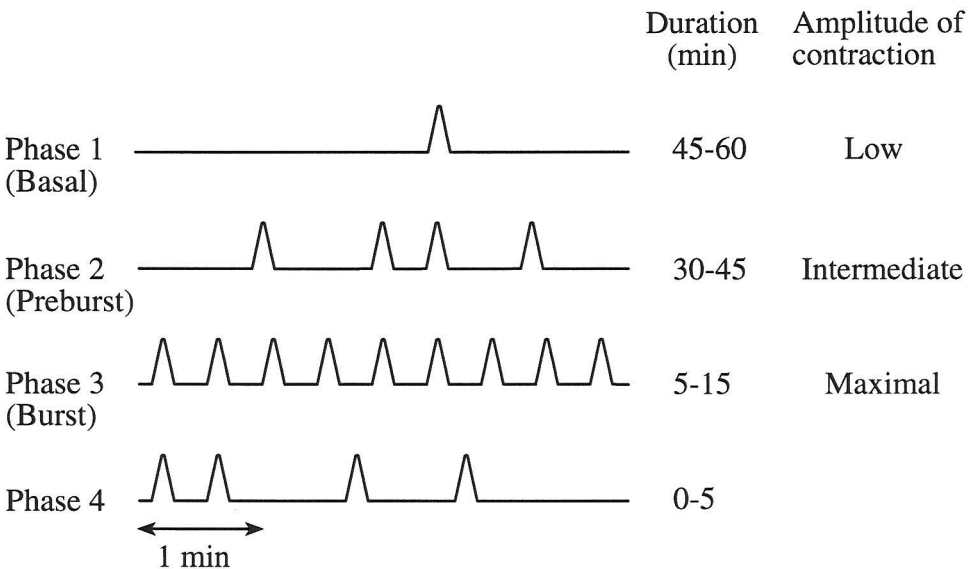


|  | Duration (min) | Amplitude of contraction |
|---|---|---|
| Phase 1 (Basal) | 45-60 | Low |
| Phase 2 (Preburst) | 30-45 | Intermediate |
| Phase 3 (Burst) | 5-15 | Maximal |
| Phase 4 | 0-5 | |

1 min

**FIGURE 4.** The four phases of interdigestive migrating myoelectric complex (IMMC) and their durations. The IMMC is usually initiated at the proximal stomach or lower esophageal sphincter. From Minami.[23]

tractions. The frequency and amplitude of the intermittent peristaltic contractions increase in Phase 2 (preburst state). Phase 3 (burst state) is characterized by a burst of giant peristaltic contractions that occur three times per minute. It is the Phase 3 contractions that remove indigestible solids from the stomach. Because of this sweeping property, Phase 3 contractions are also called "housekeeper" waves. As opposed to its action in the fed state, the pylorus remains open as a Phase 3 interdigestive contraction approaches. Phase 4 is a short transition period from Phase 3 to Phase 1. The IMMC begins in the proximal stomach and migrates aborally through the small bowel.[23] Phase 3 is repeated every 80 min to 2 h. For gastric retention devices to be useful, they must overcome the housekeeper waves and remain in the stomach in the fasted state. Each phase of the IMMC usually initiates in the proximal stomach or lower esophageal sphincter and migrates distally to the duodenum and then down the small intestine to the colon. When one Phase 3 action is arriving at the colon, another Phase 3 is beginning in the stomach.[24]

## B. Physical Properties of Oral Dosage Forms Important to Gastric Retention

The two main physical properties known to affect gastric residence time are the size and density of oral dosage forms. The effects of size and/or density of oral dosage forms on gastric emptying have been studied by various methods. The pharmacokinetic profiles of oral dosage forms with different sizes are often compared to indirectly evaluate gastric emptying (or retention). Also frequently used are direct methods such as radiography, $\gamma$-scintigraphy, endoscopy, and radiotelemetry, which provide more accurate information in terms of gastric retention. It is the pharmacokinetic data, however, that should provide the ultimate conclusion as to whether extended gastric retention provides better bioavailability for a drug.

### 1. Size of Oral Dosage Forms

Studies on the effect of particle size on gastric retention have been inconclusive. In general, it is known that indigestible solids larger than about 1 mm–2 mm are known to be held in the stomach throughout the postprandial period, after which they are emptied by cyclically recurring bursts of interdigestive gastric contractions.[24] Other studies, however, have suggested that this observation may not be generalized. Many recent studies have shown that nondigestible solid particles as large as 7 mm can be emptied from the human stomach during the postprandial period.[26,27] In the fed state, contractions in the antrum of the stomach mix and grind digestible material. Periodically waves of activity move suspended solid material to the distal antrum. The pylorus is contracted, but a small quantity of liquid chyme containing particles of suspended (food) material smaller than about 5 mm is allowed to pass through the pylorus

into the duodenum. Larger materials are returned to the body of the stomach for further digestion. This process of grinding followed by sieving by the pyloric region continues until the stomach is empty of digestible material. The gastric emptying of a nondisintegrating (large) single-unit dosage form does not normally occur until the stomach has emptied of food and the remaining undigested material is cleared by action of the IMMC. In contrast, small multiple-unit dosage forms are able to empty from a fed stomach. Since *in vivo* behavior of the multiple-unit drug-delivery system has been shown to differ from that of single-unit dosage forms, we will divide them into different categories.

## Nondisintegrating Single-Unit Dosage Forms

Khosla and Davis[32] studied gastric emptying of large tablets (7 mm, 11 mm, and 13 mm in diameter) and found that there was no significant difference in gastric emptying time of tablets in the size range of 3 mm–11 mm, while gastric residence time for 13 mm tablets was on the average 30 min–60 min longer than smaller tablets. This result suggests that indigestible solids of 13 mm or larger are less likely to be emptied from the fed stomach in man. It was proposed that the 13 mm tablets were retained for a longer period of time and emptied only during the powerful Phase 3 "housekeeper" contractions of the IMMC. Similar results were reported by other investigators.[31] Coupe et al.[33] monitored motility of the stomach and transit of indigestible large capsules by using pressure-sensitive radiotelemetry and γ-scintigraphy techniques simultaneously. The purpose of the study was to examine whether the IMMC was actually responsible for clearing larger solids from the stomach. Large radiotelemetry capsules, measuring $25 \times 8$ mm, were given to eight healthy men immediately after a light meal. In all subjects, the capsules were not emptied from the stomach during the postprandial phase (2.1 h ± 0.4 h after the meal). In six of eight subjects, the capsules emptied from the stomach (2 h–5 h after the administration) by the IMMC. In two subjects, the capsule resisted this strong interdigestive motility and remained in the stomach for 7 h in one case and more than 12 h in the other. Medium-sized single-unit dosage forms (< 10 mm in diameter) emptied from the stomach during or at the end of digestion, with a large interindividual difference as the size became larger. Not many studies are reported for dosage forms larger than 10 mm due to the impracticality of this size for oral administration. Available data suggest that even oral dosage forms of 10 mm–15 mm may not guarantee gastric retention because of significant interindividual variations.[32,33]

There is no controversy about the observation that the gastric residence time of any dosage form is prolonged in the fed state. The gastric residence time is influenced by the content of the food, with higher caloric or fatty meals delaying gastric emptying of food and dosage forms.[27,34,35] When the IMMC is responsible for emptying of indigestible dosage forms, continuous administration of a light meal has been suggested to prolong gastric residence time.[36] This, however, is an approach that defeats

the purpose of developing an oral controlled-release dosage form.

While there is no consensus about the size dependence of gastric emptying, the data in the literature suggest that, for oral dosage forms to remain in the stomach in the fasted state, their size has to be larger than 15 mm. Defining a cut-off size for gastric retention in man in the fasted condition would be very difficult, mainly due to the fact that dosage forms large enough to be retained in the stomach would be very difficult to swallow. One approach for overcomming this would be to develop superswellable dosage forms.

## Nondisintegrating Multiple-Unit Dosage Forms

Gastric emptying time of single-unit dosage forms tends to be highly variable, since premature emptying of a single-unit dosage form results in an all-or-none emptying process. To avoid variable gastric emptying with single-unit dosage forms, multiparticulate (or multiple-unit) dosage forms are often used. In multiparticulate systems, individual units can be dispersed through the stomach so that they can pass randomly through the pylorus and thus distribute widely in the GI tract. For this reason, multiparticulate systems have longer reproducible gastric residence time and less intersubject variation than do single-unit systems. Multiple-unit dosage forms are also known to have less mucosal irritation.[37]

For multiple-unit dosage forms, gastric emptying is frequently characterized as the gastric emptying half time, $T_{50\%}$, which is the time required for externally measured activity of administered multiple units reduced to half at the stomach level. The $T_{50\%}$ of 1 mm pellets was one hour in fasted conditions.[36,38] This value is in line with observations by Hardy et al.,[39] who reported that the $T_{50\%}$ values of small pellets, 0.5 mm–1.8 mm, were about one hour under fasting conditions. In fed conditions, the $T_{50\%}$ values increased to various extents, depending on the size and density of the multiple-unit dosage form and the nature (type and amount) of food. The $T_{50\%}$ value of 2 h–3 h was observed for 1 mm pellets in the fed condition by Davis et al.[36,38] O'Reilly[40] observed a $T_{50\%}$ of 3 h–4 h for particles (0.7 mm–1 mm, with a density of 1.2 g/cm$^3$) after a short lag time when taken along with or after a full meal. When pellets are co-administered with semi-solid food in addition to the light meals provided one hour prior to the administration of pellets, the $T_{50\%}$ of 1 mm pellets was extended to about 6 h in man, regardless of their density.[41]

Khosla et al.[27] reported $T_{50\%}$ for 3 mm pellets in man, ranging from 1.5 h to 3 h depending on the size of the meal given prior to administration of the tablet. In contrast, Blok et al.[42] reported that after a meal of normal size, most of the 3 mm pellets still remained in the stomach in 4 of 6 subjects longer than 4 h, whereas less than 10% of food was retained in the stomach after 3 h–4 h. The study by Meyer et al.[26] suggested that there is a gradation in the size effect rather than a precise "cut-off" value. Indigestible spheres of 5 mm in diameter emptied more slowly than 1 mm spheres. The study in man by Khosla et al.[27] suggested that neither gastric emptying nor small

intestinal transit was affected by the size of tablets in the range of 3 mm–7 mm in diameter, and nondisintegrating tablets up to an undetermined critical size can empty from the fed stomach.

It has been shown that pellets disperse quickly in the stomach of fasted man, and their emptying often follows a two-stage process with a slow first phase corresponding to a lag time, followed by rapid emptying of the particles as a bolus.[43] In the fed state, the dispersion of particles in the stomach content is slow and incomplete. The meal empties from the stomach in advance of the pellets, which start to be emptied after lag times ranging from 1.5 to 4.5 h.[43] Despite their small size, gastric emptying of small pellets may not occur concomitantly with food.[44] The emptying pattern of pellets is either linear[36,38,40] or bolus.[44]

The wide differences in the $T_{50\%}$ value are expected to result from differences in the fed condition. Depending on the type and amount of food in the stomach, pellets may mix with food to a varying extent, and this may result in different lag times and thus different $T_{50\%}$ values. It may be necessary (even if it is difficult) to define the fed state in a quantitative rather than a qualitative way that is in fact very vague.

### Inconsistent Data on Gastric Emptying in the Literature

The elaborate study designed by Coupe et al.[44] to separately monitor the behavior of food and pellets (0.7 mm–1 mm size, density 1.2 $g/cm^3$) in the stomach in man suggested that the gastric emptying patterns should not be analyzed only with averaged values. The GI transit in man exhibited large interindividual differences, and averaging the data often tends to make the characteristic tendency disappear. This may have been the reason for many conflicting data in the literature. Thus, in addition to obtaining statistical values, data should be closely analyzed individually for each subject.

## IV. PROPOSED GASTRIC RETENTIVE DEVICES

While many attempts have been made to develop gastric retentive devices, few have been successful as a platform for oral controlled-release dosage forms. The various approaches used to develop gastric retentive devices can be divided into several methods as shown in Table 5. The basic concept and suggestions for further improvements are described for each approach.

### A. Intragastric Floating Systems (Low-Density Systems)

The main concept here is to use devices in which density is lower than that of water so that the devices can float on top of the gastric juice. This is expected to prolong the gastric residence time and thus increase the bioavailability of drugs that are mainly

**TABLE 5**
**Devices Used as Platforms for Gastric Retention**

---

- Intragastric floating systems (low-density systems)

- High-density systems

- Mucoadhesive systems

- Magnetic systems

- Unfoldable, extendible, or swellable systems

- Superporous hydrogel systems

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absorbed in the upper part of the GI tract. The devices may acquire low density after administration to the stomach (Figure 5A) or possess low density from the beginning (Figure 5B).

## 1. Hydrodynamically Balanced System (HBS)

### Concept

A hydrodynamically balanced system (HBS) was the first formulation that used the floating property of a device with density lower than that of water.[45] HBS is simply a capsule containing a mixture of drug, gel-forming hydrophilic polymers (e.g., hydroxy-
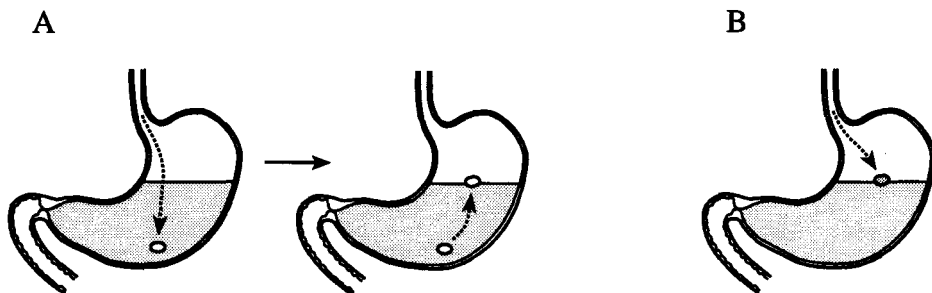
**A**          **B**



**FIGURE 5.** Devices with densities lower than 1 can be used to make systems floating in the stomach. The density of a device can be lowered after administration to the stomach **(A)**, or can be made of lower density materials from the beginning **(B)**.

propylmethylcellulose), and such other excipients as hydrophobic fatty materials (e.g., stearates).[45-51] Upon contact with gastric fluid after oral ingestion, the capsule shell dissolves and the drug-hydrocolloid mixture absorbs water and swells to create a soft gelatinous outside surface barrier. Since the relative integrity of the overall shape is maintained, the density of the system at this stage becomes < 1, mainly because of the presence of a dry mass in the center aa well as the presence of stearates, which slow down the penetration of water to the inside. As the hydrated outer layer is eroded, a new gelatinous layer is formed. During this process, the drug in the hydrated layer is thought to be released by diffusion. Figure 6 describes this process.

## Improvements to Be Made

The potential limitation of this approach is that the floating concept in an HBS is rather passive, i.e., it mainly depends on the air captured in the dry mass inside the hydrating gelatinous surface layer. The presence of a small amount of fatty material, added to impede wetting, also aids buoyancy. Because of this passivity, the buoyancy of an HBS largely depends on the characteristics and amount of hydrophilic polymer used.[52] To make a better floating HBS, many investigators tried other combinations of hydrophilic polymers (e.g., agar,[53,54] carrageenans,[53] and alginic acid,[53]) and hydrophobic materials (e.g., oil[53,54] and porous calcium silicate[55]). Floating capabilities of various excipients were also examined by Gerogiannis et al.[56,57] Since it was difficult to achieve both good buoyancy and a desirable release property, a modified version of an HBS was developed. Double layered floating systems were proposed to optimize floating capabilities and drug release profiles separately.[52,58] The drug layer
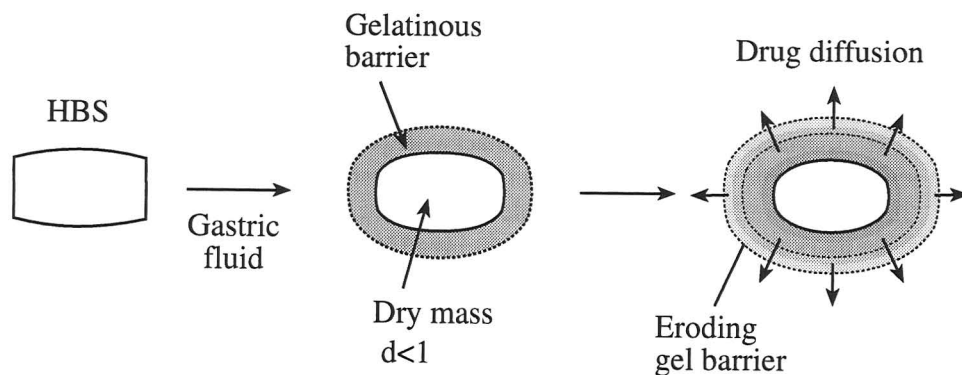


**FIGURE 6.** Description of the hydrodynamically balanced system (HBS). Diffusion of the gastric fluid to a dried HBS system results in a formation of the gelatinous polymer layer. Drug is released by diffusion and erosion of the gel barrier.

was a typical HBS and the buoyant layer comprised an excess amount (80%) of HPMC.

Floating of an HBS has been visually observed *in vivo* using endoscopy in a few human volunteers.[49] The floating HBSs were shown to have slightly longer gastric residence times than nonfloating devices.[50] In the subjects who took a meal once before administration, the capsules containing a double layered HBS were emptied from the stomach at the end of the digestive phase, i.e., in approximately 3 h. On the other hand, when the subjects were given meals before completion of the previous digestive phase, the system remained in the stomach for more than 10 h as examined by γ-scintigraphy.[52] Such a long gastric retention, however, may not be related to the floating property. The gastric residence time can be prolonged for any dosage form as long as food is maintained in the stomach. While the concept of an HBS is attractive, it has not been really developed into an effective gastric retention device, except for one commercial product. For the floating device to be useful, it has to remain in the stomach even in the fasted state. But this may be extremely difficult, since the floating system requires the presence of gastric juice, which may not be available in the fasted state. Thus, at least with the knowledge we have, the floating system has inherent limitations when used as a gastric retention device in the fasted state.

## 2. Gas-Generating Floating Systems

### Concept

Since one of the main limitations of an HBS appeared to be the lack of a good floating mechanism, systems with an improved buoyant property have been designed. The gas-generating floating systems lower density by generating gas bubbles in the matrix. Usually carbon dioxide is generated from sodium bicarbonate at an acidic pH.[59-61] For this reason, acids, e.g., citric or tartaric acid, are included in the formulation. The system may be composed of single- or multi-layers in various geometries such as membranes or spheres. The gas-generating unit can be incorporated in any of the multiple layers.[18,59,62,63] Alternatively, the gas-generating unit can be loaded inside microparticles such as ion-exchange resin beads,[60] which can be loaded with bicarbonate and coated with a semipermeable membrane. On contact with gastric juice containing hydrochloric acid, carbon dioxide is released, which causes floatation of the device.[61]

In a human study, the semipermeable membrane-coated beads showed prolonged residence times over the noncoated control during a 150 min observation period. Floatable microbeads can also be prepared using multiple layers. Figure 7 shows an example of a gas-generating microballoon system that is composed of double layers surrounding the drug reservoir.[14,15] The inner layer is made of two separate layers of sodium bicarbonate and tartaric acid, and the outer layer is a swellable membrane layer. Initially the system has a density larger than 1 and thus it sinks. As water permeates into the inner effervescent layers, sodium bicarbonate and tartaric acid are mixed together to generate carbon dioxide gas, and this lowers the density to less than 1 g/mL.
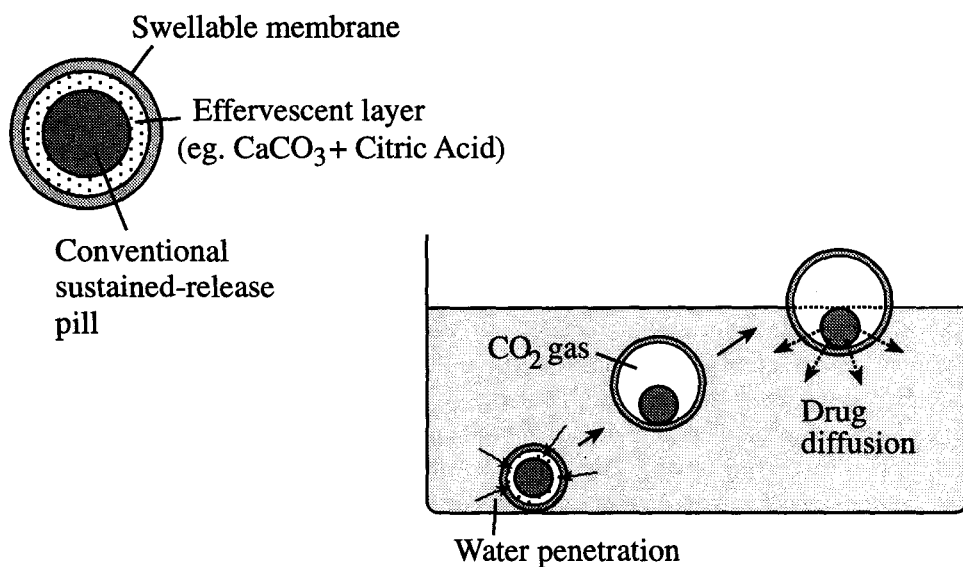
**FIGURE 7.** Structural characteristics (left) and floating mechanism (right) of the gas-generating microballoon system. The right figure shows penetration of water into the microparticle and generation of $CO_2$ to make the system float. From Ichikawa.[14]

## Improvements to Be Made

The results of *in vivo* studies employing gas generating floating systems have not been consistent. Some studies showed moderate— i.e., up to 25%—increase in bioavailability of riboflavin.[63] In a study of drug-absorption kinetics and bioavailability of acetaminophen in humans, the gas-generating formulation did not show any significantly different bioavailability from that of a regular tablet in both fasted and fed conditions.[62] In yet another human study, the bioavailability of amoxicillin trihydrate was actually reduced by 20% with the buoyant device.[18]

The main problem here is that the persistence of the buoyant property has not been carefully examined in most of the devices. For this reason, it was suggested that the initial bulk density of the dosage unit and changes of the floating strength with time should be characterized prior to *in vivo* comparison between floating and nonfloating units.[64,65] The real issue to be considered here is that all the dosage forms, whether buoyant or not, are expected to be emptied from the stomach in the fasted state by housekeeper waves. Human studies using γ-scintigraphy showed that floating capsules, or floating tablets, generally have short (< 2 h) gastric retention times under fasted conditions but may have prolonged (≥ 4 h) gastric retention times under fed conditions.[66] Thus, it appears that, as with other devices, the presence of food prolongs the gastric retention time of the floating devices. Most human studies with floating single-unit dosage forms showed the same trend in the presence of food.[49,67]

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### 3. Low-Density Core Systems

#### Concept

In this type of system, the core materials are made of low-density materials such as empty hard gelatin capsules, polystyrene foams, pop-rice grains, or concave-molded tablet shells.[68] By providing a buoyant property from the beginning, the device is thought to have a better chance to stay afloat in gastric juice. The external surfaces of the low-density materials are coated with drugs and subsequently with a variety of polymers, such as cellulose acetate phthalate or ethylcellulose, to control drug-release characteristics. Low-density systems can also be produced using hydrogel matrices, such as agar, carrageenan, and alginic acid, that contain light mineral oil.[53,54] The presence of entrapped oil and air provides the buoyancy effect.

Low density floating systems have often been prepared as microparticles. Because of the low-density core, some microparticles are called microballoons.[37,69-71] Radiographic study in humans showed that the microballoons were dispersed in the upper part of the stomach and were retained there for over 3 h against peristaltic action.

#### Improvements to Be Made

This type of device has the same limitation as any other low-density device. It may well be that gastric retention is not controlled by low density alone. Davis et al. examined the effect of density on gastric retention.[41] Their study showed that light pellets (density of $0.94$ g/cm$^3$, diameter of $0.7$ mm–$1.0$ mm) emptied from the stomach at a slightly slower rate compared to heavy pellets (density of $1.96$ g/cm$^3$, diameter of $0.7$ mm–$1.0$ mm) in three of four subjects with a large interindividual difference. Emptying of the heavy pellets conformed to a single linear function, whereas the lighter pellets showed a two-phase pattern. At early times the emptying rate of the heavy pellets was greater than that for the light pellets, which tended to float toward the fundus of the stomach. At later times the light pellets were imaged in the lower part of the stomach and then were generally emptied more quickly from the stomach than the heavy pellets. Since the density of the light pellets used in the study was only 0.94, this may not represent gastric retention of true low-density devices. However, this study points to the same problem for all dosage forms, i.e., dosage forms are emptied from the stomach in the fasted state regardless of density differences.

### 4. Intragastric Floating Systems Summary

The effectiveness of floating devices is in large part determined by the presence of enough liquid in the stomach, which requires frequent drinking of a large quantity of

water. Another limitation is that gas-generation does not guarantee subsequent floating of the device on top of the gastric juice. As described above, the results of many studies did not support the efficacy of the buoyant systems.[18,62] While these particular studies should not be used to disprove the entire concept, they indicate that improvements have to be made before the buoyancy truly prolongs gastric residence time. In many situations, there may just not be enough water in the stomach to make the devices float. Even with truly floating devices, housekeeper waves tend to remove these devices from the stomach.

Although extension of gastric residence time of low-density devices may not be easy to achieve under fasted conditions, such devices may offer an advantage over other devices in that they may prevent direct contact of undissolved drug with the stomach lining.[72] This may be a substantial advantage in using drugs that are known to damage the stomach surface.

## B. High-Density Systems

*Concept*

High-density devices utilize weight as a retention mechanism. As the density of the device is larger than that of gastric juice, the device settles down to the bottom of the stomach, as shown in Figure 8 . For veterinary applications, the high-density devices are made of heavy materials such as steel cylinders or steel balls.[73] Such devices work well in ruminants, but obviously cannot be applied to humans. There are limits to the density of oral dosage forms for humans, as well as to the size of oral dosage forms based on a high-density mechanism.

*Improvements to Be Made*

Since an early observation that the GI transit time of multiple-unit formulations was increased dramatically from 7 h to 25 h by increasing the density from 1 to 1.6,[74-76] many studies
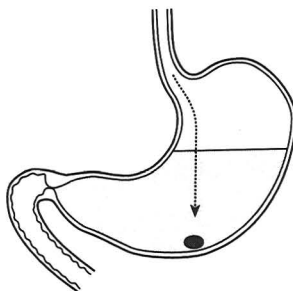


FIGURE 8. Settlement of a high-density device to the bottom of the stomach.

have been conducted to exploit this approach for increasing gastric retention time. Unfortunately, however, subsequent studies found that, under their experimental conditions, higher density single-unit devices did not really extend gastric residence time.[77]

In many experiments, specific gravity was shown to have only a minor effect on gastric emptying.[78-80] It should be noticed, however, that the density of the particles used in most experiments was less than 2, and the size of the particles was small, i.e., much less than 10 mm. It may be necessary to use particles of a density much higher than 2 and larger sized devices to really observe the desired effect of high-density devices. Until then, it may not be fair to conclude that high-density devices are not effective in gastric retention.

A dog was brought to a small animal clinic at Purduc University.[81] It has swallowed a stone a few centimeters in diameter. According to x-ray imaging, the stone remained in the stomach for a few days and then emptied. It thus appears that high-density systems should work, if the density and size of the devices are optimized, but gastric emptying would depend on the position of the high-density device in the stomach at the time of the housekeeper wave. Obviously more work is necessary, but the high-density approach should not be considered invalid.

## C. Mucoadhesive Systems

### Concept

The concept of mucoadhesives (or bioadhesives) is that an oral dosage form in the stomach can stick to the mucosal surface of gastric tissue. Once the dosage form firmly sticks to the mucosal surface, its gastric residence time is expected to be prolonged until it is removed by turnover of mucins. Figure 9 shows this simple, and yet highly innovative concept. The study on mucoadhesive was initiated by a paper by Park and Robinson in 1984.[82] Professor Gilbert Banker, then at Purdue University, also studied mucoadhesive oral dosage forms at about the same time. Since then, numerous investigators have been involved in studying fundamental aspects and potential applications of mucoadhesive dosage forms.[83-92] Of all the studies done in this area, the best mucoadhesive still remains slightly crosslinked poly(acrylic acid), which is commercially available as polycarbophil and Carbopol®. Polycarbophil and Carbopol® are poly(acrylic acid) loosely cross-linked with divinyl glycol and ally sucrose, respectively. Due to differences in crosslinking density, polycarbophil is water-insoluble, while Carbopol® picks up so much water that it appears to be water-soluble. Polycarbophil is a granular substance that swells to 1 mm–3 mm in diameter.[93]

### Improvements to Be Made

Despite the excellent mucoadhesive properties of polycarbophil and Carbopol®, gastric emptying studies using these products in animals and in humans have shown rather
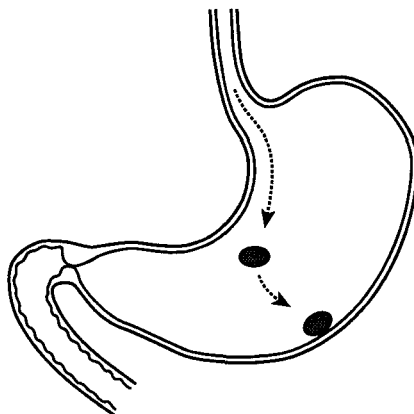
**FIGURE 9.** Attachment of a mucoadhesive dosage form to the mucus layer in the stomach.

disappointing results. In a typical study on mucoadhesives by Harris et al.,[94,95] 50 μL of suspension or liquid in capsule formulation containing bioadhesive polymers was orally administered to rats. Polycarbophil and Carbopol showed the delayed gastric emptying in rats with $T_{50\%}$ over 3 h in the fasted condition; $T_{50\%}$ for a control group was 1 h–1.5 h. In man, however, different results were obtained when polycarbophil or Carbopol was mixed with radioactive resins for γ-scintigraphic observation. The $T_{50\%}$ values in fasted stomachs were 36 min, 82 min, and 25 min for polycarbophil, Carbopol, and control formulations, respectively. Other researchers who mixed polycarbophil with radioactive pellets in human testing also observed similar results.[96] The data from many laboratories suggest that gastric residence time of mucoadhesive formulations in human is not substantially longer than with control formulations.

The main problem with polycarbophil and Carbopol is that they are good adhesives that stick to almost everything they come in contact with. For this reason, they also interact with gelatin released from gelatin capsules, or with soluble proteins and mucins present in the stomach. Any such interactions would easily deactivate an ability to stick to the mucus layer.[96]

In studying mucoadhesives, especially crosslinked poly(acrylic acid), one needs to understand the mechanism of their bioadhesiveness. Poly(acrylic acid) interacts with mucins and other biomolecules through numerous hydrogen bondings provided by carboxyl groups of poly(acrylic acid), as shown in Figure 10. For this reason, poly(acrylic acid) is only bioadhesive when it exists in a protonated form, i.e., only when the pH is lower than the pKa of the polymer. Figure 11 shows the mucoadhesive strength of polycarbophil when attached to the gastric tissue of rabbits at various pH values.[97] According to the figure, the pKa of polycarbophil can be estimated to be around 5. This means that polycarbophil and all poly(acrylic
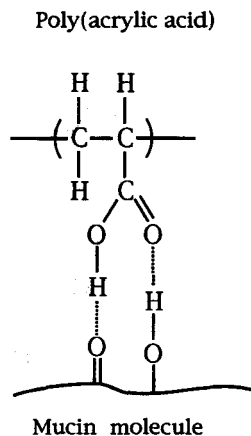
Poly(acrylic acid)



Mucin molecule

**FIGURE 10.** Interaction between poly(acrylic acid) and mucin molecules through numerous hydrogen bonding.

acid)–based mucoadhesives are adhesive only at pHs lower than 5. As shown in Figure 11, polycarbophil is most mucoadhesive at pH 4 and below. At physiological pH, poly(acrylic acid) exists in an ionized form and it is not bioadhesive. This
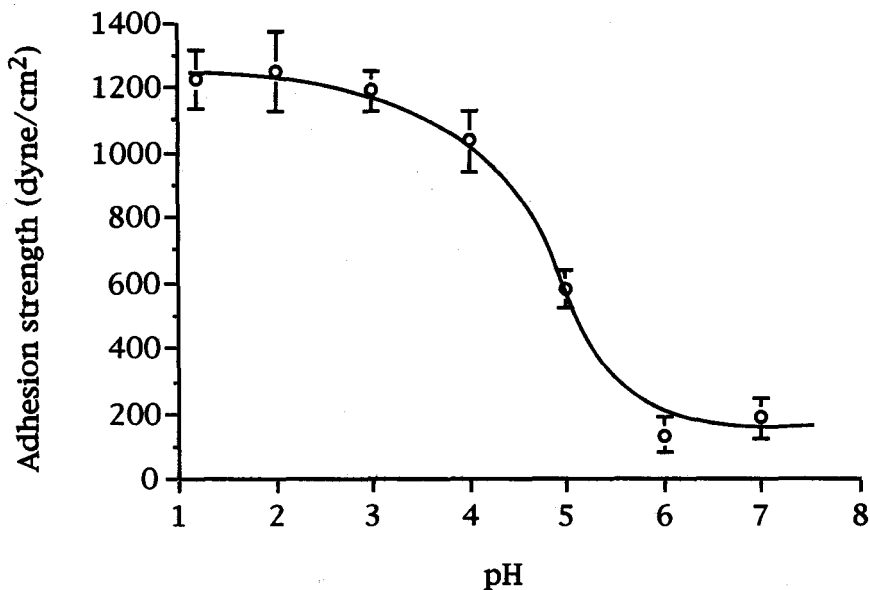


**FIGURE 11.** Mucoadhesive strength of polycarbophil to rabbit gastric tissue as a function of pH. From Park and Robinson.[97]

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information has been available in the literature since 1985,[97,98] but not many researchers appear to be aware of it.

To further develop mucoadhesive gastric retention devices, it is necessary to find polymers with a specific mucoadhesive property, i.e., polymers that are adhesive only to the mucus layer and to nothing else. Currently known mucoadhesives, however, do not show any specificity toward mucin—they bind to other substrates as well. This nonspecifity makes it difficult to formulate practical dosage forms. If a mucoadhesive, e.g., polycarbophil, is applied to conventional dosage forms such as tablets or capsules, the delivery of these mucoadhesive-coated dosage forms to the stomach will be difficult, since they will bind to fingers, tongues, and the esophagus surface. It may be suggested that mucoadhesive dosage forms be contained in gelatin capsules, but gelatin upon dissolution will interact with polycarbophil and the mucoadhesiveness of polycarbophil will be lost as mentioned above.

Even if the polycarbophil is delivered to the stomach intact, soluble mucin will interact with polycarbophil before it has a chance to interact with the mucus layer. For a mucoadhesive dosage form to be practical, mucus layer–specific bioadhesives have to be found.

## D. Magnetic Systems

### Concept

Magnetic dosage forms are usually constructed from a hydrophillic matrix tablet and from osmotic systems containing a small internal magnet.[99–102] In one system, a permanent magnet (e.g., magnesium ferrite) 5 mm in diameter and 2 mm thick was placed in the center of the tablet. The final dimensions were 10 mm in diameter and 5.5 mm in height. An extracorporeal magnet (6 × 4 × 2 cm) was placed and fixed over the position of the stomach to control gastrointestinal transit of the dosage form.[101] Drugs delivered by magnetic dosage forms, e.g., cinnarizine,[101] acetaminophen,[103,104] and riboflavin,[100] showed improved bioavailability. It was suggested from absorption rate–time profiles that the variation in pharmacokinetics was caused by a 3 h delay in gastric emptying time. The data in this study show that a 3 h delay in gastric emptying increased the AUC two-fold.[104]

In a separate study, gastric retention of a magnetic dosage form was monitored by use of a pH-sensitive radiotelemetric capsule, also known as the Heidelberg capsule.[105] Small magnets were attached to the Heidelberg capsule and this model dosage form was administered to humans. The dosage forms transited to the alkaline area (i.e., intestine) within 2.5 h after administration in all subjects without an external magnetic source. On the other hand, gastric residence time of model dosage forms were longer than 6 h in most of the test subjects with the external magnets positioned on the stomach level. Fujimori et al.[101,103,104] reported similar results. In their studies, double-layered magnetic tablets were prepared. Drug—acetaminophen or theo-

phyllin—and magnetic component—fine ferrite ($\gamma$-$FeCO_3$) particles—were contained in separate layers. Two layers were bonded together by cyanoacrylate-type adhesives. After administration of the magnetic tablet, a magnetic field or a permanent magnet was externally applied at the stomach level of dogs for 8 h. Results showed that bioavailability of the drugs was significantly increased (near 90% increase) when external magnetic control means were applied.

## Improvements to Be Made

While the concept of this approach is clean and obviously works, its practical application is rather difficult. The exact positioning of the extracorporeal magnet to the magnetic dosage forms in the stomach by each individual may not be easy. The benefit of the magnetic dosage form would be all-or-none depending on whether the external magnet is in the right place for the duration of drug delivery. Asking patients to pay attention to the exact position of the magnet is not any better than asking them to eat something every two hours to maintain the fed state. For this approach to be useful, better and easier systems for applying the magnetic field need to be developed.

## E. Unfoldable, Extendible, or Expandable Systems

### 1. Systems Unfolding in the Stomach

### Concept

Systems that unfold in the stomach have one or more noncontinuous compressible retention arms. The retention arms are initially folded to make the whole system smaller. With the arms folded, the system can be fit into gelatin capsules or the folded arms can be fixed by a gelatin band. In the stomach, the compressed or folded retention arms are expanded to make the whole system too large to resist gastric transit.[106] One example of this type of devices is shown in Figure 12.

### Improvements to Be Made

Since the device has to be emptied after all the drug is released, it is important to connect the compressible retention arm to the drug-delivery module using a biodegradable polymer. One of the problems noted with this type of device is that such biodegradable polymers may start degradation, albeit to a very small extent, during the folded state in storage; for this reason, the retention arms may not open up in the stomach. No animal studies have been done to determine how long they can stay in the stomach. In addition, even if they work as planned, the design of this type of device
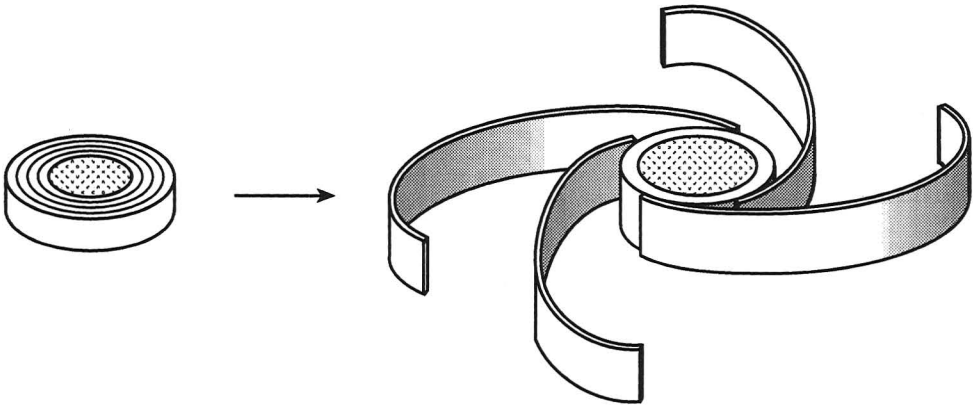
**FIGURE 12.** The system with the coiled arms (left) can unfold the arms (right) in the stomach. The expanded form is expected to resist gastric retention. From Curatolo and Lo.[107]

is so elegant that it requires a great deal of attention to produce, and so they may not be cost-effective.

## 2. Systems Extending to Complex Geometric Shapes

### Concept

Studies have shown that devices that extend in the stomach to certain geometric shapes can prolong gastric retention time.[108-113] The geometric shapes include a continuous solid stick,[108] a ring,[109] and a planar membrane.[110] Since these devices should be small in the beginning for easy swallowing, they have to be compressible to a small size and expandable to a size large enough to prevent emptying through the pylorus. In one study, the longest length of the final dimension of devices varied from 2 cm to 5 cm while the shortest length was around 2 cm.[110] Figure 13 shows an example of this type of approach.

### Improvements to Be Made

In beagle dogs, some of these devices showed extended gastric residence time (longer than 24 h) in the fasted condition.[107,111-113] In humans and larger dogs, however, the devices emptied from the stomach much faster.[113] The median gastric residence time of a tetrahedron-shaped device in man was 6.5 h and 3 h in the fed and fasted states,
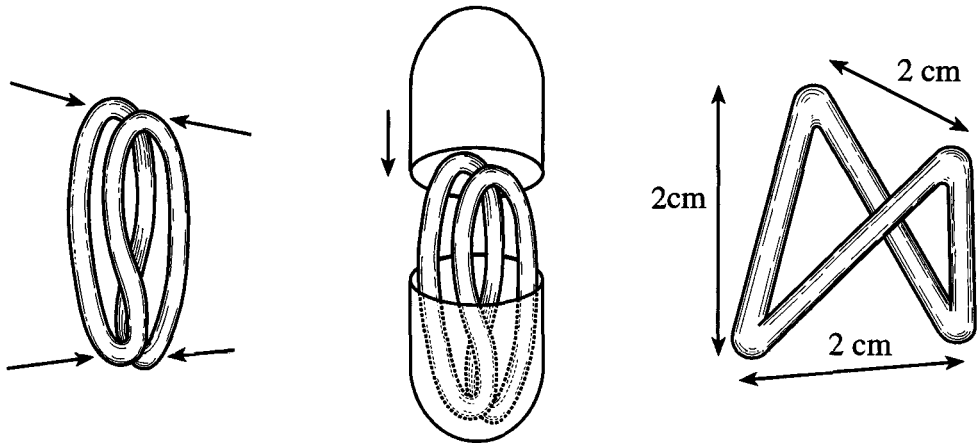
**FIGURE 13.** The tetrahedral form of the device is compressed (arrows in the left figure) for encapsulation (center). In the stomach, the preferred tetrahedral form (right) is restored for extended gastric retention. From Caldwell et al.[108]

respectively. This study points to the need of a gastric-retention study in humans. More importantly, it also points to the fact that this approach is based on trial and error; for this reason, it is rather difficult to optimize a geometric shape for maximum gastric retention in humans. While an increase in flexural moduli resulted in an increase in gastric retention, it alone does not appear to be a dominating factor for extended gastric retention.[112] In addition, to make the system removable after use from the stomach, biodegradable systems have to be used; this may cause the same problem as observed with the unfolding systems.

## 3. Systems Expanding to Larger Sizes

### Concept

The idea here is to make devices that are small enough for easy swallowing but expandable upon contact with gastric juice to a size sufficient to cause retention of the device in the stomach (i.e., to a size too large to pass through the pylorus). The concept is shown in Figure 14. This type of device is made to a size slightly larger than the diameter of the pyloric canal, that is, about 1 cm to 4 cm, usually 2 cm in humans, until completion of the prescribed therapeutic regimen.[114] Because the systems have to be removed from the stomach eventually, they have to be made either degradable or deflatable.

The main component of swellable systems is the agent that causes swelling of the device. Swelling can be achieved by several methods. First, one can employ hydrogels that swell upon contact with water.[115,116] Second, the swelling can also be achieved by wrapping the osmotic expanding agents (such as sugars, sugar derivatives, and salts)
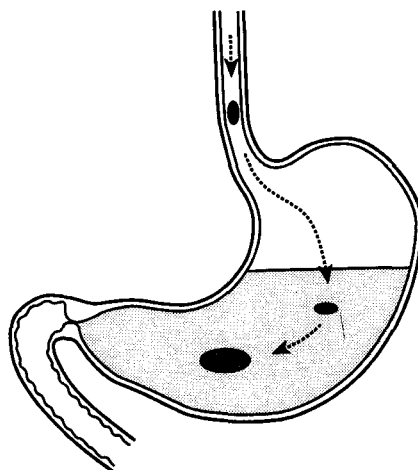
**FIGURE 14.** The expandable device can swell in the stomach either by absorbing water from the gastric juice or by evaporation of solidified or liquefied gas present in the device.

or swellable expanding agents (such as swellable resins and hydrocolloids) with semi-permeable membranes or polymer membranes that are substantially nonhydratable but permeable to both drug and body fluids.[117] Third, solidified or liquefied gas at ambient temperature can be used as a swelling agent.[114,118] The liquefied or solidified gas in a compartment will vaporize at physiological temperature to produce gas that inflates the device from a collapsed state to an expanded state. Gases that have a boiling point lower than 37 °C can be used. Examples of such gases are diethyl ether (boiling point of 34.6 °C), methyl formate (boiling point of 31.5 °C), tetramethyl silane (boiling point of 26.5 °C), iso-pentane (boiling point of 27.9 °C), perfluoropentane isomers (boiling point of 31.0 °C), n-pentane (boiling point of 36 °C), and diethenyl ether (boiling point of 28 °C).[118] Figure 15 shows an example of this type of approach. As shown in the figure, the extent of swelling is rather modest.

### Improvements to Be Made

Devices that are designed to imbibe fluid and expand two- to fifty-fold have been proposed, but they were not tested in animals,[116] so their effectiveness in gastric retention remains to be seen. One of the major problems with the hydrogel approach is that swelling of the dried hydrogels, especially in the size of ordinary tablets and capsules, takes a few hours, and they may be emptied from the stomach even before reaching a fully swollen state. Second, the increase in size after swelling may not be large enough to make the device retained in the stomach over an extended period. For emptying from the stomach, the hydrogels have to be degradable or erodible. For systems utilizing osmotic or swellable expanding agents, a substantial portion of the expanding agents inside the polymer envelope has to be removed from the device; the removal of gases based on
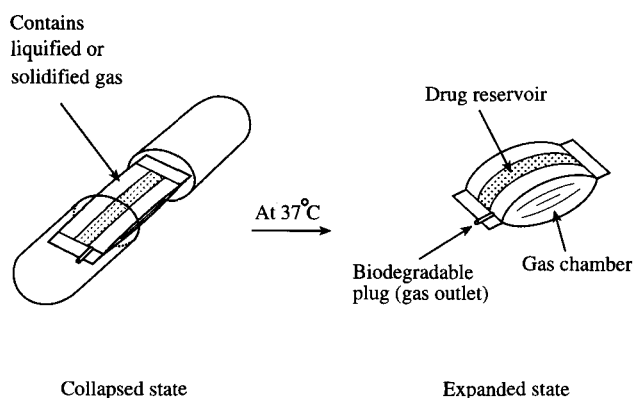
Contains
liquified or
solidified gas

Drug reservoir

At 37°C

Biodegradable
plug (gas outlet)

Gas chamber

Collapsed state

Expanded state

**FIGURE 15.** An example of an expandable device based on gas evaporation. The expanded device will be deflated upon removal of the plug by biodegradation. From Michaels et al.[118]

vaporized gases will be an even bigger problem. These variables have not been worked out to make an effective gastric retention device, and no animal experiments have been done to show efficacy of this approach. As with unfolding systems, the manufacturing of these devices may be much more difficult than with other dosage forms.

## F. Superporous Biodegradable Hydrogel Systems

This approach is based on the swelling of unique hydrogel systems. The principal difference of these devices from those described earlier is that the extent of swelling of superporous hydrogels is far beyond that obtainable by other systems. The swelling ratio (volume of the swollen gel/volume of the dried form) can easily be over 1,000, compared with the only two- to fifty-fold increases obtained with other expanding systems. Because of their unique superswelling property, superporous hydrogels will be treated separately. To understand this system, it is necessary to understand how hydrogels and superporous hydrogels are different.

### 1. Hydrogels and Superporous Hydrogels

Both hydrogels and superporous hydrogels can be made either by crosslinking water-soluble polymer chains or by polymerizing hydrophilic monomers in the presence of crosslinking agents. The main difference between the two types of hydrogels is pore size.

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## Conventional Hydrogels

Conventional hydrogels made by bulk polymerization lead to production of a glassy, transparent polymer matrix that is very hard. When immersed in water, such a glassy matrix swells to become soft and flexible. Although it allows the transfer of water and some low-molecular-weight solutes, this kind of swollen polymer matrix (i.e., hydrogel) is considered nonporous. The pores between the polymer chains are in fact the only spaces available for mass transfer, and the pore size is within the range of molecular dimensions (a few nanometers or less).[119] Hydrogels that are prepared by solution polymerization can be considered porous, and the pore size depends on the type of monomer, the amount of diluent in the monomer mixture (i.e., the monomer–diluent ratio), and the amount of crosslinking agent.[120] As the amount of diluent (usually water) in the monomer mixture increases, the pore size also increases up to the micrometer range.[119] Hydrogels with an effective pore size in the 10 nm–100 nm range and in the 100 nm–10 mm range are called microporous and macroporous hydrogels, respectively.[119,121] In practice, hydrogels with pores up to 10 mm can be described as either microporous or macroporous hydrogels. When the hydrogels are dried, they become glassy and no pores are observed even by scanning electron microscopy. Figure 16A shows the surface of dried hydrogel cut in half. No pores are seen on the dried macroporous hydrogels. Due to the hydrogel's glassy nature, absorption of water into the gel by diffusion is a very slow process. For dried hydrogel the size of ordinary tablets, the swelling takes several hours.

## Superporous Hydrogels

Superporous hydrogels are a new type of hydrogel that have numerous supersize pores inside.[122-124] Figure 16B shows dried superporous hydrogels observed by scanning
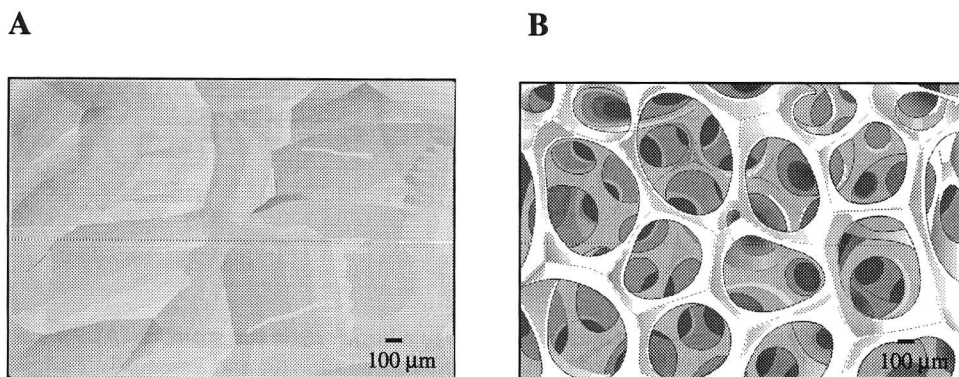
**A**

**B**



**FIGURE 16.** Representative images of conventional hydrogels **(A)** and superporous hydrogels **(B)** based on the SEM pictures.

electron microscopy (SEM). Superporous hydrogels have numerous pores while conventional hydrogels show no pores throughout the matrix even under SEM. The size of pores in superporous hydrogels is larger than 100 mm, usually in the range of several hundred micrometers, and can be up to the millimeter range. Even after drying, the pores of the superporous hydrogels remain connected to each other to form capillary channels. Because of this, dried superporous hydrogels can swell extremely fast upon contact with water and can swell to a very large size. Unlike conventional hydrogels, superporous hydrogels can swell to an equilibrium size in less than a minute regardless of size. It is this fast swelling property that is important in the application of hydrogels as a gastric retention device.

## 2. Superporous Hydrogel Systems

### Concept

The main concept here is to utilize the superswelling properties of superporous hydrogels to extend gastric retention time. The superporous hydrogels can also be made biodegradable, e.g., degradable by pepsin in the stomach. Thus, as shown in Figure 17, the dried superporous hydrogel formulation in an ordinary capsule, which can be easily swallowed, swells to a size up to several centimeters, which is too large to be emptied from the stomach. As drug is released or after all the drug is released, the superswollen hydrogel degrades and eventually empties from the stomach. As mentioned above, the swelling ratio of superporous hydrogels is in the range of several hundred at a minimum and can be much higher than 1,000. This means that each dimension can be increased 10 times.

About a decade ago, enzyme-digestible swelling hydrogels were developed for
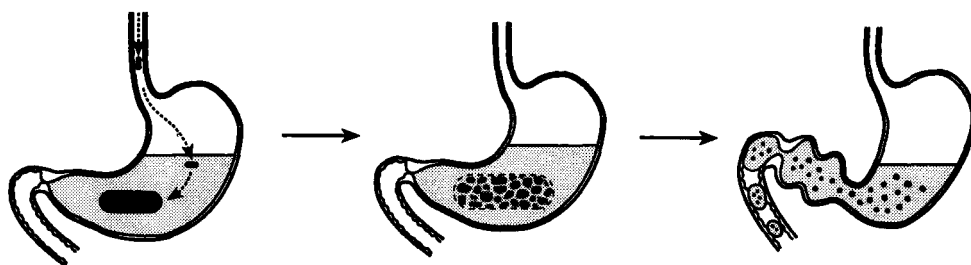


**FIGURE 17.** A dried superporous hydrogel swells to a huge size in the stomach **(A)**. As the drug is released, the swollen hydrogel can undergo degradation **(B)** and eventually is emptied from the stomach **(C)**.

potential application as a gastric retention device for oral drug delivery.[125] Subsequent animal studies showed that the swelling hydrogels could remain in the canine stomach for up to 60 h as determined by direct visualization using ultrasound, x-ray, and fluoroscopic imaging techniques.[126] The enzyme-digestible swelling hydrogel formulation was used to deliver flavin mononucleotide (FMN) for up to 50 h.[127] FMN is known to be absorbed only from the upper small intestine. Thus, the blood concentration of FMN maintained for longer than 24 h (up to 50 h) was due to gastric retention of the hydrogel in the stomach. When flavin mononucleotide was administered in a capsule without the hydrogel device, the blood level decreased to zero within 6 h. One problem with using swelling hydrogels in this study was that dried hydrogels (which are in a glassy state) did not swell fast enough in the stomach. Thus, when dried hydrogels were administered to dogs, they were all emptied in about 30 min. Other large objects such as magnetic stirring bars, a few centimeters in length, were also emptied in less than 30 min.[127] Others also observed that large nondigestible objects, such as nondisintegrating radiotelemetry capsules (or Heidelberg capsules) 7 mm in diameter × 20 mm in length with a density of 1.5, were readily emptied (in about 30 min) from the stomach.[128] The dried hydrogels were partially swollen for two hours before administration of the hydrogel formulation to avoid premature emptying. Since then, attention has been focused on developing superporous hydrogels that swell in less than a minute so that swelling kinetics do not pose a problem.

Hydrogels have remained in the stomach for more than 24 h even in the fasted state due to their unique properties.[126] Hydrogels are flexible and yet maintain a certain mechanical strength. As we examined gastric retention of various types of hydrogels, we noticed that they were under the continuous influence of gastric contractions.[127] Figure 18 shows how hydrogels remain in the stomach despite continuous gastric contractions pushing the hydrogel to the pylorus. Due to their slippery and flexible nature, hydrogels could escape gastric contractions.[126] The gastric contraction that initially



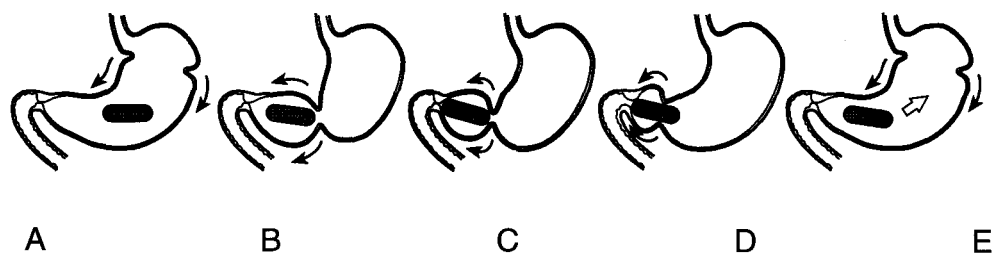A          B          C          D          E

FIGURE 18. A sequence showing the movement of a swollen hydrogel to the pylorus by gastric contractions and retropulsion back to the body of the stomach as visualized by ultrasound and fluoroscopic imaging. From Shalaby et al.[126]

pushed the hydrogel to the pylorus (A–C) slipped over the surface of a hydrogel to push the hydrogel back into the body of the stomach (D). This process was repeated (E).

### Improvements to Be Made

There are several properties that the superporous hydrogel formulation should possess in order to function as gastric retention devices. They are fast swelling, large size, surface slipperiness, and mechanical strength. For human applications, these factors need to be optimized. In dogs, hydrogels stayed in the stomach withstanding housekeeper waves when their size was about 2 cm in diameter $\times$ 2 cm in length, or larger.[126,127] The use of superporous hydrogels allows a dosage form that is small enough for easy swallowing and becomes large enough for gastric retention after swelling. According to Hougton et al., the maximum gastric pressure in the fasted and fed state, following a solid or a liquid meal, ranges from 80 mmHg to 100 mmHg in humans.[129,130] Thus, any superporous hydrogel dosage form should have mechanical strength to withstand such a pressure. To eliminate problems associated with the weak mechanical strength of highly swelling hydrogels, superporous hydrogel composites that maintain high mechanical strength even after fast swelling to a large size were developed.[124,131] While many parameters that are thought to be important for gastric retention have been worked out for superporous hydrogel systems, it still remains to be seen whether they would work in humans as well as in dogs. Only after human trials can further improvements be made.

## V. FUTURE POSSIBILITIES

### A. New Gastric Retention Devices

Oral dosage forms without gastric retention platforms all empty into the intestine during and shortly after food is removed from the stomach. Gastric retention devices can extend gastric retention even after food is emptied until the housekeeper wave appears. Most gastric retention devices currently available seem to work well until the housekeeper wave arrives. We have shown that superswelling hydrogels can overcome the housekeeper waves in dogs.[124] It is not yet known, however, whether it would still be effective in humans. While currently available approaches, with further improvements, may achieve long-term gastric retention even in the fasted condition in humans, a new generation of gastric retention devices (that may be based on radically new ideas) needs to be developed. Whatever form they may take, they must be able to overcome the repeated IMMC in the fasted state in humans. This will require more understanding of the IMMC, especially about the forces that gastric retention devices may experience. In addition other information, such as what could interrupt or prevent the

IMMC, or what could induce fed state–like motor activities, could be highly useful in the development of new gastric retention devices.

## B. Combination Approaches of Available Systems

One could combine two or more different approaches described in this review. For combination approaches, however, one must make sure that combining different approaches makes scientific sense. For example, combining the floating approach with the mucoadhesive approach is not desirable since it creates conflicting requirements. The floating devices work best in the presence of abundant gastric juice, which may make the device nonmucoadhesive. Various components in the gastric juice would foul the mucoadhesive property of the dosage form even before it has a chance to interact with the gastric mucus layer.

Considering the suggestion that the large size (> 2 cm) may be necessary for effective gastric retention, increasing the density of the swelling devices substantially (e.g., to a density of 5) may have a better chance of long-term gastric retention than either method alone.

## C. Saturation of Small Bowel Receptors for Retardation of Gastric Emptying

Regulation of gastric emptying of food begins as soon as the evacuated material has accumulated in the intestine to the point where any one of numerous stimuli (e.g., volume and chemical components in the chyme) associated with the chyme reaches threshold value.[132] Gastric emptying is known to be affected by various factors of the meal, such as volume, acidity, osmolarity, density, caloric content, and food type (fat, protein, or carbohydrate). The meals with higher volume, higher osmolarity, higher density, and/or higher caloric content tend to stay in the stomach longer. High acidity is also known to retard gastric emptying. Food containing fat or certain amino acids is known to retard gastric emptying by the action of small bowel receptors.[23] While it may not be easy to control these factors using oral dosage forms, it may be possible to affect gastric emptying by releasing from oral dosage forms compounds that are known to retard emptying, such as L-tryptophan,[132] food excipients (e.g., fatty acid[59,133,134]), or a pharmacological agent (e.g., propantheline[59]). This approach may not be practical for several reasons, including lack of knowledge about the exact quantity of these compounds that would be effective for retardation of gastric emptying.

## D. Induction of Fed State–Like Motor Pattern

One feasible approach for extending gastric retention time may be to induce the fed state using the gastric retention device itself. The exact amount and type of food necessary to induce a postprandial digestive pattern in humans has not been determined

yet. Thus it is not known at this point what kind of gastric retention devices have to be prepared to induce the fed state. Russell and Bass showed that 90 g of hydrated acid form of polycarbophil (equivalent to 12 g of dried polycarbophil) elicited fed state–like antroduodenal motility.[93] The 90 g polycarbophil meal delayed the Phase 3 activity for the entire 4 h test period. The fact that polycarbophil elicited a typical, fed-state motor pattern is significant since it suggests that the duration of the postprandial antroduodenal motor pattern can be markedly influenced solely by the size of a meal. It is also significant to notice that large spheres (with no water absorbing property) neither elicit fed state–like motility nor delay the reappearance of burst activity.[30] This strongly suggests that superporous hydrogels can elicit a fed-state motor pattern or delay the reappearance of the IMMC. Superporous hydrogel is expected to function better than polycarbophil particles, since superporous hydrogel is one large unit that has a higher swelling ability than any other known hydrogels. The bulky and semi-solid nature of the superporous hydrogel is expected to interrupt or delay the IMMC pattern, and thus increase gastric retention time in human. The main question here is what volume of superporous hydrogel would be necessary to induce the fed state–like activity.

## VI. OPTIMIZATION OF GASTRIC RETENTION DEVICES FOR HUMAN APPLICATIONS

The literature is full of conflicting information. Gastric retention devices that work in one laboratory often prove not to work in others. When a proposed gastric retention device doe not work, the immediate conclusion drawn by the study is obviously that the system does not work. As we reviewed the literature, we have noticed a few things. First of all, no study has been done comprehensively to conclude whether any gastric retention device is truly working or not. Most of the studies that showed that a proposed system did not work were often based on inadequate controls and an inadequate number of volunteers. While the studies may have produced negative results, these results were hardly sufficient to conclude that the system did not work.

When the IMMC activity was studied in human volunteers by Thompson et al. in 1980,[135] 24 healthy volunteers participated. Each volunteer swallowed a pressure-sensitive radio telemetry capsule that was suspended on a thread so that it could be stationed in the proximal small intestine. The results showed that the IMMC in humans was highly irregular compared with the very regular pattern found in dogs. They studied 20 more subjects with careful control of the timing of food only to find the same high variation. From further studies, they showed that stress was an important modulator of gut motility.[136] The lesson here is that there is too much variation in human volunteers and it is unrealistic to derive any conclusion from a gastric retention study involving only a handful of human volunteers.

In addition to high variability of human volunteers, the results of animal studies

should be extended to human applications with caution. Some studies have reported that the beagle dog may not be a good animal model for studying GI transit because of the dog's longer digestive period and delayed onset of IMMC compared to man.[137,138] This indicates that those systems that work well in animals, e.g., dogs, may not work well in humans. This does not, and should not, mean that the devices that are working well in animals do not work in humans. This simply means that the devices have to be optimized for human application. The most rational and professional approach for advancing the gastric retention field is to identify the reasons why a particular system failed and suggest ways to improve upon it. As long as the proposed system is based on sound concepts, whether the device would work or not depends on how to optimize the system for human applications.

We have great hope that a long-term gastric retention device for human application will be developed in the near future. As presented here, each gastric retention system approach has its own unique concept and each requires further improvements to be effective. Progress will only be possible if all the researchers in the field work together to analyze a concept, test it, and find ways to overcome limitations. Only after we accomplish long-term gastric retention devices can the full benefits of controlled-release technologies be realized for oral controlled-release dosage forms.

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