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Controlled-Release Drug Delivery Systems for Prolonged Gastric Residence: An Overview

A. A. Deshpande,[1]* C. T. Rhodes,[1] N. H. Shah,[2] and A. W. Malick[2]

[1]*Department of Pharmaceutics, University of Rhode Island, Kingston, Rhode Island 02881, USA*
[2]*Pharmaceutical R&D, Hoffman–La Roche, Nutley, New Jersey 07110, USA*

INTRODUCTION

Oral ingestion is the most convenient and commonly used method of drug delivery. More than 50% of drug delivery systems available in the market are oral drug delivery systems. These systems have the obvious advantages of ease of administration and patient acceptance. One would always like to have an ideal drug delivery system that will possess two main properties: (a) It will be a single dose for the whole duration of treatment. (b) It will deliver the active drug directly at the site of action. Unfortunately, such ideal systems are not available. Thus scientists try to develop systems that can be as close to an ideal system as possible. This has stimulated the development of systems such as topical delivery systems and bioadhesive systems. Attempts to develop a single-dose therapy for the whole duration of treatment has focused attention on controlled- or sustained-release drug delivery systems. "Sustained release" describes a drug delivery system with delayed and/or prolonged release of drug. It also implies delayed therapeutic action and sustained duration of therapeutic effect. "Controlled release" implies a predictability and reproducibility in the drug release kinetics (1,2). In other words, sustained-release dosage forms provide medication over an extended time period whereas controlled-release systems attempt to control drug concentrations in the target tissue. Thus we can say that these two systems are different, and we cannot consider all sustained-release systems as controlled-release systems (3). They are primarily used to ensure patient compliance and to improve efficacy of drugs. Increased safety and decreased side effects of drugs help in achieving these objects. Such systems are mainly useful for drugs with narrow therapeutic windows where minimum fluctuations in plasma levels are desired (4). The controlled- and sustained-release drug delivery systems have more flexibility in dosage design than the conventional drug delivery systems. Thus the main purpose for developing these systems is to enhance the safety of a product to extend its duration of action. There are many disadvantages of these systems such as longer time to achieve therapeutic blood levels, more variation in bioavailability, enhanced first-pass effect, and dose dump-

*Current address: School of Pharmacy, University of Geneva, CH-1211, Geneva 4, Switzerland.

ing. These systems are usually more expensive than the conventional systems (5). Since these products are made for the population at large, and not for an individual, they may result in higher or lower steady-state drug level in different individuals. If the therapeutic range of a drug is broad enough, it may not cause any problems (6). In spite of their disadvantages, research is continued in this area as there is much scope to further improve currently available systems.

This article reviews the controlled-release drug delivery systems that can be retained in stomach for a long time. Such retention systems are important for drugs that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach. If the drugs are poorly soluble in intestine due to alkaline pH, gastric retention may increase solubility before they are emptied, resulting in improved bioavailability. Such systems are advantageous in improving gastrointestinal absorption of drugs with narrow absorption windows as well as for controlling release of the drugs having site-specific absorption limitations. Such systems are useful in cases like absorption of albuterol where drug is best absorbed in the stomach (7). Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time, thereby resulting in improved bioavailability for some drugs. For levodopa, gastric emptying controls its delivery at the site of absorption, which is proximal small intestine. In this case it will be useful if gastric emptying can be controlled to achieve maximum effect of the drug (8). β-Lactam antibiotics when administered in conventional forms are absorbed rapidly to produce transient peaks in serum drug levels. For such antibiotics, gastric retention systems would be useful as they would delay gastric emptying and release drug at a slower and constant rate (9).

Such systems cannot be used in the case of drugs like aspirin and other nonsteroidal anti-inflammatory drugs that induce gastric lesions or for drugs that are unstable in the acidic environment of stomach. Many times it is difficult to incorporate a drug in such gastric retention systems. The retention of these systems depends on many factors such as gastric motility, pH, and presence of food. It is not easy to design and fabricate a system that can overcome all these difficulties.

In spite of all these reservations about such systems, they have generated enormous interest. This article reviews physiological and anatomical factors which play important roles in design of gastric retention drug delivery systems and various gastric retention systems developed so far.

STOMACH

Anatomy

The main function of the stomach is to store food temporarily, grind it, and then release it slowly into the duodenum. The stomach is an important site of enzyme production. Due to its small surface area, very little absorption takes place from the stomach. It provides a barrier to the delivery of drugs to the small intestine (10,11).

The stomach is located below the diaphragm. Various factors such as volume of food ingested, posture, and skeletal build affect the exact position of the stomach. Anatomically it can be divided into four regions, namely, fundus, body, antrum, and pylorus. The main function of fundus and body is storage, whereas that of antrum is mixing or grinding. The fundus adjusts to the increased volume during eating by relaxation of the fundal muscle fibers. The fundus also exerts a steady pressure on the gastric contents, pressing them towards the distal stomach. To pass through the pyloric valve into the small intestine, particles should be of the order of 1–2 mm. The antrum does this grinding (10).

Physiology

Factors such as pH, nature and volume of gastric secretions, and gastric mucosa play an important role in drug release and absorption.

pH

Environmental pH affects the performance of orally administered drugs. The pH of stomach in fasted condition is about 1.5 to 2, and in fed condition usually it is 2 to 6 (11). A study conducted in male and female subjects in the Netherlands obtained surprising results. It was found that many subjects in this study had basal pH higher than 6 and many values were between 7 and 9 (12). A large volume of water administered with an oral dosage form changes the pH of stomach to the pH of water initially. This change occurs because the stomach does not have enough time to produce a sufficient quantity of acid before emptying of liquid from the stomach. Thus it does not improve dissolution of basic drugs. Basic drugs will have a better chance to dissolve in a fed condition rather than in a fasted condition (13).

Volume

The resting volume of the stomach is about 25–50 ml (11). Gastric volume is important for dissolution of dos-

age forms in vivo. Meyer et al. conducted an experiment to study effect of gastric pH on the absorption of controlled-release theophylline dosage forms in human beings. During this experiment they measured the gastric fluid volume of each subject. They estimated mean gastric fluid volume in normal and achlorhydric subjects. The mean volume ± SD recovered by continuous gastric aspiration over three consecutive 15-min time periods was 61 ± 51 ml in achlorhydric subjects and 98 ± 38 ml in normal subjects. The authors did not think that such a large volume difference in gastric secretions would significantly affect in vivo dissolution of drugs as each dose was administered with 180 ml of water (14).

Gastric Mucosa

Simple columnar epithelial cells line the entire mucosal surface of the stomach. Mucous, parietal, and peptic cells are present in the body of stomach. These cells are associated with different functions. The parietal cells secrete acid whereas the peptic cells secrete precursor for pepsin. The surface mucosal cells secrete mucus and bicarbonate. They protect the stomach from digestion by pepsin and from adverse effects of hydrochloric acid. As mucus has a lubricating effect, it allows chyme to move freely through the digestive system (10).

Gastric Secretion

Acid, pepsins, gastrin, mucus, and some other enzymes are the secretions of the stomach. Normal adults produce a basal secretion up to 60 ml with approximately 4 mmol of hydrogen ions every hour. The volume of this secretion can go beyond 200 ml and 15 to 50 mmol of hydrogen ions when stimulated. Pure parietal secretion is a mixture of hydrochloric acid and potassium chloride. Histamine stimulates acid secretion through the H_2 receptors located on gastric mucosa. Another potent stimulator of gastric acid is the hormone gastrin. Peptides, amino acids, and distention of stomach stimulate its release. The absorption of vitamin B_{12} from the ileum requires the intrinsic factor, which is continuously secreted by the stomach. The mean thickness of mucus in human stomach is 140 μm. It is continuously digested from surface. Generally it takes 4 to 5 hours for mucus turnover. It protects the gastric mucosa from pepsin and acid in the stomach (10).

Effect of Food on Gastric Secretion

On average the daily intake of a normal adult is 3 to 4 kg of food and drink. In response to this stimulus, the gut secretes an additional 5 liters of fluids. The volume produced within the first hour of eating can be twice that of the meals. A distinct pH gradient exists in the stomach after a meal. The contents of the body of stomach are neutralized but the antrum remains relatively acidic in nature. Thus ingestion of food is the major stimulus to acid secretion in stomach. This effect is more pronounced if the meal has a high protein content. It is interesting to know that the protein content of a meal has the maximum buffering capacity. Wilson and Washington have found that a meal can increase the pH to 3 to 5, and foods such as milk can raise it to over pH 6 (10).

Gastric Motility

The stomach produces coordinated movements of the gastric contents due to three layers of smooth muscles. These layers are outer longitudinal muscle layer, inner circular muscle layer, and an oblique layer (10).

It is difficult to control the environment of a dosage form in the gastrointestinal tract at all the times following ingestion. The existing motility pattern at the time of administration affects the performance of oral dosage forms. The motility patterns are different in digestive or fasted and interdigestive or fed conditions (11).

There are four phases of stomach movement in the fasted condition. During the digestive phase, motility results in constant emptying of chyme from the stomach into the duodenum. This movement occurs similar to a wave. The interdigestive myoelectric cycle, or migration myoelectric complex (MMC), is an electrical activity observed during fasting phase. It is divided into four phases. In phase 1 (basal phase), there is no contraction or secretion. It lasts for about 40 to 60 min. In phase 2 (preburst phase), there are irregular contractions and bile secretion. During this phase the pressure rises to about 5 to 40 mm of Hg during contractions. It lasts for about 20 to 40 min. Mucus discharge takes place in phase 3 (burst phase). During this phase, the frequency and amplitude of contraction is at the peak. This a short phase that lasts for about 4 to 6 min. During this phase, the baseline pressure increases substantially. The fourth phase is a short transitional period of 0 to 5 min between phases 3 and 1 (10,11).

This phase activity moves along the esophagus, stomach, antrum, duodenum, jejunum, ileum, and cecum. It takes about 2 hr for this phase to move from stomach to ileocecal junction. This phase acts as a cleaning phase, and thus it is also called the "housekeeper wave" (10,11).

In fed conditions, only one phase is present. This phase is present as long as there is food in the stomach. It consists of regular and frequent contractions. These contractions are not as severe as those in the third phase of fasted motility pattern (11).

Gastric Emptying

Particle size (15–17) and feeding state (18,19) strongly affect the residence time of particles in stomach. Some other factors affecting gastric emptying are as follows: type of meal and its caloric content, volume, viscosity, and coadministered drugs. The rate of gastric emptying primarily depends on the caloric contents of the ingested meal (20). It does not differ for proteins, fats, and carbohydrates as long as their caloric content is the same. Hunt and Stubbs (21) have shown that nutritive density of a meal helps to determine the rate of gastric emptying. Generally an increase in acidity, osmolarity, and calorific value slows down gastric emptying (22). Stress increases gastric emptying rate whereas depression slows it down (23). Generally females have a slower gastric emptying rate than males. Age and obesity also affect gastric emptying. Gastric emptying of dosage forms is different in fasted and fed conditions.

Liquids in Fasted and Fed Conditions

Volumes of liquids affect gastric emptying of liquids. Liquids empty exponentially; that is, the larger the volume, the faster the emptying. Gastric emptying of small volumes like 100 ml or less is governed by the MMC cycle whereas large volumes of liquids like 200 ml or more are emptied out immediately after administration (11). Weisbrodt et al. (24) have shown that 50% of a large volume of saline solution leaves the stomach in about 8–12 min. Fluids at body temperature leave the stomach more rapidly than either warmer or colder fluids. Studies have shown that gastric residence time can be increased by the ingestion of a meal prior to administration of liquids (25). Horton et al. (26) have shown that local or systemic effects of various drugs and the physical orientation of the body affect gastric emptying.

Solids in Fasted and Fed Conditions

Tablets or capsules do not have any significant calorific value. Therefore the stomach treats them as an indigestible material. The gastric residence time of such units is highly variable in the fasted condition. Gastric emptying of such units depends on MMC. Park et al. (27) have shown that gastric emptying of tablets was not affected by the physical properties of tablets. It is known that particle smaller than 2 mm in size are emptied from the stomach quickly.

In the fed state, the stomach handles particles of different sizes in different ways. Wilson et al. (28) have shown that in the case of large, nondisintegrating units, gastric emptying becomes more predictable when they are administered after a light meal. Khosla et al. (29) showed that large, nondisintegrating tablets empty from the stomach during the digestive phase. Meyer et al. (30,31) have shown that spheres empty from the stomach filled with food as a function of their diameter. They have also shown that this relationship ends when the diameter drops below 1 mm. When Fischer et al. (32) conducted an investigation on gastrointestinal passage of pellets, they found that on an empty stomach, the typical emptying times $T_{50\%}$ were 50 to 80 min. In the case of fed stomach, gastric emptying time was 188 min. Davis et al. (33,34) have shown that pellets were emptied from stomach in 119 and 285 min when administered after a light and a heavy breakfast, respectively.

DOSAGE FORMS

The design of controlled-release dosage forms should take into account three important criteria, viz., drug, delivery, and destination. Preformulation studies help in studying the physicochemical properties of drugs. These properties include pK_a, pH, solubility, stability, and incompatibility (35). The solubility of a compound affects the choice of a controlled-drug delivery system. If the compound has very low solubility (e.g., less than 0.01 mg/ml), it is inherently sustained. A drug has to cross a variety of biological membranes in order to produce a therapeutic effect when it is administered to the gastrointestinal tract. Thus partition coefficient of a drug is important in determining penetration of these membrane barriers by the drug. Compounds with very low partition coefficients will not easily penetrate these membranes, resulting in poor bioavailability. Acid–base hydrolysis and enzymatic degradation attack orally administered drugs. Compounds such as propantheline are unstable in small intestine. This results in decreased bioavailability when administered in controlled-release delivery form (3).

Today, a wide range of gastrointestinal controlled-delivery systems is available in the market. Generally the nature of the delivery system depends on the physicochemical properties and dose of the drug, the purpose for controlling drug release, and constraining physiological and pathological factors (35).

In case of oral drug delivery systems, the first destination is the gastrointestinal tract. From here the drug is absorbed and is taken to site of action. Thus the physiology of the gastrointestinal tract has a direct effect on the design of controlled-release delivery systems. In addition, effects of disease conditions and coadministered drugs also affect the design (35).

It is noteworthy that there is a relative paucity of controlled drug delivery systems of proven value for use by the oral route. Though much research has been conducted to develop controlled-release delivery systems, very few systems which are retained in stomach for a long time have been developed so far. These systems mainly consist of swelling and expanding systems, floating and inflating systems, and bioadhesive systems.

Swelling and Expanding Systems

One way to retain a dosage form in the stomach is by increasing its size. The stomach discharges its content through the pylorus into intestine. If the dosage form can attain a size larger than that of the pylorus, it can be retained in the stomach for a long time. Of course, it is not possible to swallow a dosage form of such a large size. Thus it should attain this large size once it is in the stomach. This large size should be achieved fairly quickly; otherwise the dosage form will be emptied through the pylorus. In addition, this enlarge form should not block the pylorus. Such a dosage form should also be strong enough to be able to withstand the powerful waves from the stomach.

Various patents are available for these swelling forms. Johnson et al. (36) have a patent on swelling tablets or capsules. These tablets or capsules contain a reaction product of gelatin and *N*-acetyl-homocystein thiolactone as a component. After swallowing, these products swell to an extent that prevents their exit from stomach through the pylorus. Mamajek and Moyer (37) used an expandable envelop containing a drug and an agent. This agent expands when gastric fluid permeates through the envelope. Thus this device enlarges and remains in the stomach for a long time. Theeuwes and Urquhart (38) describe a device containing a hydrogel. This device swells 2- to 50-fold in the stomach. Small pills containing drug are released from this device for gastric or intestinal absorption. These patents do not always describe the process by which these devices disintegrate or are emptied from stomach.

Caldwell et al. (39–41) have described gastric retention devices in the shape of a solid stick figure, a ring figure, and a planar figure. These devices are made up with at least one erodible polymer. They are erodible in the presence of gastric juices so that they lose their enlarged or expanded forms after a predetermined time. Examples of erodible polymers that can be used practically are cellulosics such as Klucel, polyacrylates such as Eudragit E, polylactones, and polyanhydrides. Examples of nonerodible polymers are polyolefins, polyamides, and polyurethanes. A drug can be dispersed within an erodible matrix or within a nonerodible matrix. It can also be fastened to the retention device in the form of a controlled-release drug module. An example of such a module is a miniature constant-flow pump. The inventors administered these devices to dogs in gelatin capsules. So far, these devices have not been converted for human use.

Cargill et al. tried a different approach to delay gastric emptying of drugs (42). They carried out the studies in dogs. They studied the importance of physical characteristics such as size, shape, and flexibility on gastric emptying. They molded cloverleaf, disk, string, and pellet shapes from a Silastic elastomer. They fabricated tetrahedron and rigid ring shapes from blends of polyethylene and polyethylene or ethylene:vinyl acetate. These devices were loaded in capsules and administered to dogs with 15–50 ml of water. It was observed that the tetrahedron made with low-density polyethylene remained in the stomach for longer periods than other shapes of similar size. Gastric retention of rigid rings was affected by their size. Disk and cloverleaf shapes showed poor gastric retention. The stomach eliminated strings and pellets fairly rapidly. Though this study does not give the final solution to the problem of gastric retention, it is definitely thought provoking. More work can be done in this area to develop a gastric retention system (42).

Floating Systems

A floating dosage unit is useful for drugs acting locally in the proximal gastrointestinal tract. These systems are also useful for drugs which are poorly soluble or unstable in intestinal fluids. The floating properties of these systems help in retaining these systems in the stomach for a long time. Various attempts have been made to develop a floating system. This system will float on gastric contents for the desired time period. During this time period drug will be released from this system. After the release of a drug, the remnants of the system will be emptied from the stomach. Watanabe et al. (43) developed a floating system. They used empty globular shells with a lower density than that of gas-

trointestinal fluid. This enabled the shell to float on the gastric fluid and thus achieved prolonged residence in stomach. They used polymers such as polystyrene. Though this system was able to float on gastric fluid, it was difficult to incorporate drugs into such a system. Mitra (44) described a system containing multilayered polymer films. This system contained a drug in matrix along with sealed air pockets. Sheth and Tossounian (45) developed a system of drug and hydrocolloid mixture. This mixture swells and forms a soft gelatinous mass which floats on the top of gastrointestinal fluid when it comes in contact with it. Bolton and Desai (46) developed another floating system with a gel-type matrix. They incorporated light oil with drug in this system. Cook et al. (47) increased the efficacy and reduced the side effects with a hydrodynamically balanced capsule containing iron salts. Khattar et al. (48) used this system for delivery of propanolol hydrochloride.

Oth et al. developed a bilayer floating capsule for misoprostol. There were two layers in a capsule: a release layer and a floating layer. The floating layer consisted of Methocel K4M, lactose, Aerosil 200, and magnesium stearate. The release layer consisted of various combinations of Methocel K4M, K100, drug, hydroxypropylmethylcellulose and Pharmacoat 606 and 603. Dissolution and γ-scintigraphic studies were conducted on these capsules. Large quantities of high-viscosity polymer were incorporated to form a strong viscous layer. This helped in maintaining the integrity of the floating layer for a long time. The drug release layer consisted of a gelling agent. This helped in avoiding disintegration and prevented delivery of large particles containing drug into intestine, thus reducing side effects. There was complete erosion of the release layer during dissolution. The mean gastric residence time was 199 ± 69 min after a light breakfast. After meals, gastric residence time was found to be 618 ± 208 min. The study indicated that the two layers did not separate during drug release. This study has shown that a bilayer floating capsule of sufficient size is a viable system for delivery of drugs at the proximal gastrointestinal tract level (49).

Thanoo et al. developed floating polycarbonate spheres (50). They used aspirin as a sample drug. In order to reduce the side effects of aspirin, especially in high-dosage therapy such as is needed in arthritis, scientists have tried to develop a system that can overcome these problems. Low dosages for a long time can help in reducing gastrointestinal irritation. They prepared hollow drug-loaded polycarbonate microspheres using a solvent evaporation process. In vitro release studies were conducted in simulated gastric and intestinal fluids. Drug entrapment efficiency of the microspheres depended on initial drug loading. Initial drug loading also affected the particle size distribution of the microspheres. Increased loading of the drug resulted in increased release rate. Particle size affected the release patterns. Initially faster release was observed from the smaller particles, and from larger particles in the later stages. These scientists have shown that polymers such as polycarbonate can be used to form hollow microspheres that can float on gastric fluids and release drug for a long time to reduce the side effects of drugs like aspirin (50).

Mazer et al. (51) investigated the cause for slow absorption kinetics of a floating capsule of isradipine. Isradipine is a calcium channel blocker. They also investigated effect of food on intragastric behavior of these floating capsules. Davis et al. (52) have shown that gastric residence time of floating and nonfloating dosage forms is longer under fed conditions than under fasted conditions. Muller-Lissner et al. (53) concluded that presence of food is the most important factor affecting gastric residence time. Thus these authors studied isradipine capsules under both fasted and fed conditions. In vitro release studies showed that floating capsules remained intact and floating during the 8-hr run. Only 56% of drug was released from these capsules at the end of 8 hr. Slow erosion of the hydrocolloid matrix was the rate-limiting factor for the drug release in vitro. Under fasted conditions there was a transient rise and fall in drug levels. Floating capsules exhibited much lower peak gastric juice drug levels than the normal capsules. Floating capsules displayed sustained-release plasma levels. A high-fat breakfast strongly influenced gastric juice drug levels from the floating capsules. Under fed conditions both gastric juice drug levels and plasma drug levels exhibited lag times. Under fed conditions there was a close relationship between the intragastric behavior and the plasma levels. In vitro data showed an excellent correlation with in vivo absorption kinetics under fasted conditions. This showed that a slow erosion from the capsule surface was responsible for slow drug release, and not the floating characteristics of the capsule. These scientists have shown that floating alone is not responsible for the sustained release of a drug. They found that in case of an isradipine floating device, maximum release of the drug took place in the colon, and not in the stomach as desired. Thus floating devices are not applicable in all cases. They have

also shown that floating does not invariably increase gastric residence time (53).

Agyilirah et al. studied the effect of fasted and fed conditions on gastric retention of balloon dosage forms (7). They compared the gastric emptying time of the balloon dosage forms and the uncoated nondisintegrating tablets. In 0.1 M hydrochloric acid at 37°C, the coating from tablets separated from the core. It formed a balloon around the core. As a result, the entire tablet started floating. This flotation occurred within 15 min of dropping the tablet into the medium. The balloon tablet was three to six times larger than the original one. These tablets released 88% of drug over 8 hr during in vitro dissolution studies. The drug release occurred through diffusion. Under fasted conditions the balloon type and the nondisintegrating types of tablets were emptied from stomach quite quickly. Under fed conditions the balloon tablets remained in the stomach for a longer time than the nondisintegrating tablets. They remained in the stomach for about 6 h more than the nondisintegrating tablets. The balloon tablets floated more quickly in fasted condition than in fed condition. This could be due to presence of high-viscosity gastric contents during fed condition (7).

All these floating types of devices function on the basis of buoyancy whereas inflating balloon-type devices achieve enlarged size by converting part of the device into gaseous form.

Bioadhesive Systems

Another approach to increase gastric residence time of the dosage forms is to bind them to gastric mucosa or epithelial cell surfaces. Park et al. (54) studied a broad spectrum of polymers for their bioadhesive properties. They concluded that anionic polymers have better binding capacity than neutral or cationic polymers. Longer et al. showed that performance of a drug such as chlorothiazide improved when it was formulated in a bioadhesive dosage form (55). Chlorothiazide is an antihypertensive drug. It is slightly soluble in water. It is a good candidate for development of a bioadhesive dosage form due to its physicochemical and biological properties. Polycarbophil–albumin beads containing the drug were prepared. In vitro dissolution studies and in vivo studies on rats were conducted. Albumin beads released the drug slowly over period of 8 hr. Polycarbophil did not affect the drug release. In vivo studies showed that 90% of the polycarbophil–albumin beads administered remained in the stomach even after 6 hr. Autopsy showed that bulk of the polymer was binding to the surface closely. Rinsing could not easily remove it easily. The polycarbophil–albumin beads improved the bioavailability of the drug by 1.95 times (55). It is not easy to relate this study to human beings.

In case of bioadhesive systems, the mechanism of adhesion is thought to be the formation of electrostatic and hydrogen bonding at the mucus–polymer boundary. The adhesion is favored by rapid hydration. These bioadhesive systems do not seem to be a very feasible solution as this bond formation is prevented by the acidic environment and thick mucus present in the stomach. High turnover of mucus adds to the difficulties in retaining a bioadhesive system at the site.

All the above systems claim to increase gastric residence time of the drugs. All of them have some drawbacks and most of them show reliable retention for only a few hours.

CONCLUSION

This review has covered the information about controlled- or sustained-release drug delivery systems having prolong gastric residence time. A perfect system which will be retained in the stomach for a long time has not yet been developed. Such gastric retention systems are useful for drugs with slow and incomplete intestinal absorption, drugs that have local effects in stomach such as antacids, and for other reasons. The research in this area is ongoing and it will not be long before an improved system is developed.

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