DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 10, pp. 1019–1028, 2004

Gastroretentive Delivery Systems: A Mini Review

R. Talukder and R. Fassihi*

Temple University School of Pharmacy, Philadelphia, Pennsylvania, USA

ABSTRACT

Various attempts have been made to develop gastroretentive delivery systems. For example, floating, swelling, mucoadhesive, and high-density systems have been developed to increase gastric retention time of the dosage forms. It is known that differences in gastric physiology, such as, gastric pH, and motility exhibit both intra- as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behavior. Nevertheless, some floating devices have shown promising results. In this paper, the gastric physiology and the reported intragastric delivery systems have briefly been presented.

Key Words: Intragastric; Proximal GI; Drug delivery; Floating devices; Bioadhesive; Mucoadhesive; High-density system.

INTRODUCTION

Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substance. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract,[1] and drugs that are less soluble in or are degraded by the alkaline pH may benefit from prolonged gastric retention.[2,3] In addition, for local and sustained drug delivery to the stomach and proximal small intestine to treat certain conditions, prolonged gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability and therapeutic efficacy, and possible reduction of dose size.[4–6] It has been suggested that prolonged local availability of antibacterial agents may augment their effectiveness in treating *H. Pylori* related peptic ulcers.[7] Moreover, it has been reported that the bactericidal effects of clarithromycin, garcinol, and reveratrol are time and concentration dependent.[8] Menon et al.[9] have compared the absolute bioavilabilty of furosemide in dogs from commercial products and a floating dosage form. Higher bioavailability from floating dosage form

*Correspondence: R. Fassihi, Temple University School of Pharmacy, 3307 N. Broad St., Philadelphia, PA 19140, USA; Fax: (215) 707-3678; E-mail: reza.fassihi@temple.edu.

DOI: 10.1081/DDC-200040239
0363-9045 (Print); 1520-5762 (Online)

than the non-floating commercial products of furosemide has been attributed to the fact that the upper gastrointestinal tract is the primary site of absorption for the drug.

Gastroretentive delivery systems (GRDS), however, are not suitable for drugs that may cause gastric lesions, e.g., non-steroidal anti-inflammatory agents. Also, the drug substances that are unstable in the strong acidic environment of the stomach are not the suitable candidates to be incorporated in such systems. In addition, these systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.

However, it is recognized that there are many physiological constraints which may limit development of such delivery system. Following is a brief description of the physiological considerations pertaining to designing GRDS.

PHYSIOLOGICAL CONSIDERATIONS

The intrinsic properties of the drug molecule and the target environment for delivery are the major determining factors in bioavailability of the drug. Factors such as pH, enzymes, nature and volume of secretions, residence time, and effective absorbing surface area of the site of delivery play an important role in drug liberation and absorption. In stomach there are several types of cells that secrete up to 2–3 liters of gastric juice daily. For example, goblet cells secrete mucus, parietal cells secrete hydrochlororic acid, and chief cells secrete pepsinogen. The contraction forces of the stomach churn the chyme and mix it thoroughly with the gastric juice. The average length of the stomach is about 0.2 meter, and the apparent absorbing surface area is about 0.1 m^2 (Table 1). A brief survey of relevant physiological features that pose challenge to the development of an effective gastroretentive delivery system is presented below.

Gastric pH

The gastric pH is not constant rather it is influenced by various factors like diet, disease, presence of gases, fatty acids, and other fermentation products.[10] In addition, the gastric pH exhibits intra-as well as inter-subject variation. This variation in pH may significantly influence the performance of orally administered drugs. Radiotelemetry, a noninvasive device, has successfully been used to measure the gastrointestinal pH in human. It has been reported that the mean value of gastric pH in fasted healthy subjects is 1.1 ± 0.15.[11–13] On the contrary, the mean gastric pH in fed state in healthy males has been reported to be 3.6 ± 0.4,[14] and the pH returns to basal level in about 2 to 4 hours. However, in fasted state, basal gastric secretion in women is slightly lower than that of in men.[15,16]

Gastric pH may be influenced by age, pathological conditions and drugs. About 20% of the elderly people exhibit either diminished (hypochlorohydria) or no gastric acid secretion (achlorohydia) leading to basal pH value over 5.0.[17] Pathological conditions such as pernicious anemia and AIDS may significantly reduce gastric acid secretion leading to elevated gastric pH.[18,19] In addition, drugs like H_2 receptor antagonists and proton pump inhibitors significantly reduce gastric acid secretion.

The pH in the proximal duodenum may rise as high as 4 pH units from the stomach.[20] This increase in pH is caused by the bicarbonate secreted by the pancreas and the duodenal mucosa that neutralize the acidic chyme peristalsed from the stomach. The mean pH value in fasted duodenum has been reported to be 5.8 ± 0.3 in healthy subjects[21] while the fasted small intestine has been observed to have a mean pH of

Table 1. Salient features of upper gastrointestinal tract.

Section	Length (m)	Transit time (h)	pH	Microbial count[a]	Absorbing surface area (m^2)	Absorption pathways[b]
Stomach	0.2	Variable	1–4	$<10^3$	0.1	P,C,A
Small intestine	6–10	3 ± 1	5–7.5	10^3–10^{10}	120–200	P,C,A,F.I,E,CM

[a]Numer of microorganisms per gram of gastrointestinal contents.
[b]P, Passive diffusion; C, Convective or aqueous channel transport; A, Active transport; F, Facilitated transport; I, ion-pair transport; E, entero-or pinocytocis; CM, Caveolin mediated transport.
Adapted from Refs. [11,12,14,17,18,22,23] and [33].

6.0±0.14.[13] Passing from jejunum through the mid small intestine and ileum, pH rises from about 6.6 to ~7.5.[22]

Gastric pH is an important consideration in selecting a drug substance, excipients, and drug carrier(s) for designing intragastric delivery systems

Gastrointestinal Motility and Transit Time

Based on fasted and fed states of the stomach, two distinct patterns of gastrointestinal motility and secretions have been identified. In the fasting state, the stomach usually contains saliva, mucus, and cellular debris. The fasted state is associated with some cyclic contractile events commonly known as migrating myoelectric complex (MMC). Liquid components easily pass through the partially constricted sphincter. On the contrary, the large undigested materials are retained by an ''antral-sieveing'' process and are retropulsed into the main body of stomach and remain in the fed state. In the fed state, gastric contractions move the contents towards the antrum and the pyloric sphincter. Usually a series of interdigestive events take place in the stomach. However, feeding disrupts this cycle causing a period of irregular contractile pattern.[23] The MMC, which governs the gastrointestinal motility pattern has been described as an alternating cycles of activity and quiescence. Apparently there are four consecutive phases of activity in the MMC.[24–28]

Phase I: It is a quiescent period lasting from 30 to 60 minutes with no contractions.

Phase II: It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.

Phase III: This is a short period of intense distal and proximal gastric contractions (4–5 contractions per minute) lasting about 10 to 20 minutes; these contractions, also known as ''house-keeper wave,'' sweep gastric contents down the small intestine.

Phase IV: This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase I. A simplified schematic representation of the motility pattern, frequency of contraction forces during each phase, and average time period for each period is shown in Fig. 1.

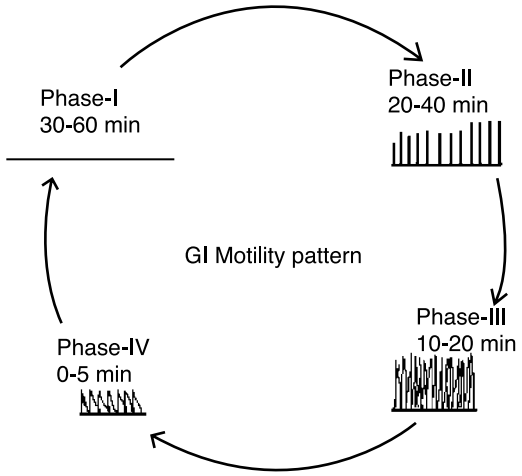

Figure 1. Schematic representation of interdigestive motility pattern. (Adapted from Ref. [25].)

The different phases originating in the foregut continue to the terminal ileum cycle in about 2 hours. Therefore, when one phase III reaches the terminal ileum, another begins in the stomach and duodenum.[29] As mentioned before, feeding disrupts this cycle resulting in a period of irregular contractile activity, which may last for many hours (i.e., 3 to 4 hours). Thus frequent feeding may prolong gastric retention time.

One of the important factors that influence the gastric emptying is the caloric content of the meals. Usually fats tend to form an oily layer on the other gastric contents, as such, fatty substances are emptied later than the others.[30] Also, increased acidity and osmolality slow down gastric emptying. Stress appears to cause an increase in gastric emptying rate, while depression slows it down. In general, women and elderly have a slower gastric emptying rate than men and young people respectively.[31,32] In addition, exercise, and body posture may influence the gastric emptying.[33] However, Mojaverian et al.[34] have observed no significant effect of posture (standing vs. flat on back) on gastric residence time (GRT).

It has been reported that drugs taken before meals usually exit from the stomach within an hour; but when taken after meals, the GRT especially for non-disintegrating tablets may be as high as 10 hours. Nevertheless, it has been suggested that small size tablets of less than 7 mm in diameter may exit from the fed stomach regardless of its emptying pattern.[35] However, the two most important parameters that influence the gastric emptying of sustained release dosage forms are the size of the delivery system, and the state of the

stomach, i.e., whether the drug is administered in fed or fasted state.[36] In the fasted state, the gastric emptying of large single unit dosage forms is erratic and it is dependent on the time of arrival in the stomach in relation to activity of MMC.[37]

As far as the size is concerned, it has been reported that differences in gastric emptying of various sizes tablets up to 11 mm in diameter, under fed conditions, are insignificant. However, the much discussed 2mm cutoff size for gastric emptying of indigestible solids during the digestive phase in canines may not be applicable to human.[38] In addition, the relationship between the tablet size and its gastric emptying appear to vary significantly among the subjects.[39] Also, the non-disintegrating systems of a size in excess of the mean diameter of the pylorus (in man, 12.8±7 mm) appear to be retained in the stomach for as long as the digestive phase is maintained.[40]

Multiple-unit systems containing 1-mm pellets have been found to pass through the constricted pylorus with a gradual emptying.[41] When the pellets are administered with a light meal, an initial short lag phase followed by a linear emptying pattern is observed.[36] On the other hands, when encapsulated pellets are taken with a heavy meal, prolonged gastric emptying of pellets is observed.[42] However, in most cases, tablets are emptied before all the pellets are emptied. This phenomenon has been explained by two theories. Upon dispersion in the stomach, the pellets may be lodged within the folds of stomach wall prolonging their gastric emptying time. Secondly, gastric contractions during the digestive mode may empty large particles fortuitously as compared to the smaller ones.[32] Under certain circumstances, especially in fasted state, multiparticulate systems may empty from the stomach as a bolus.[41]

Therefore, the state of the stomach, i.e., fed or fasted state in relation to drug administration, is the primary consideration for modulating gastric residence time. Along with that, the original size and where applicable expanded size after administration of the dosage form play a significant role in its GRT.

APPROACHES TO PROLONG GASTRIC RESIDENCE TIME (GRT) OF DRUG DELIVERY SYSTEM

Various devices such as mucoadhesive, swelling, high-density, and floating systems have been developed to increase GRT of a dosage form. Physiological features of the upper gastrointestinal tract pose a considerable challenge to develop such systems. Nevertheless, in vivo studies of certain systems have shown promising results.

Mucoadhesive Systems

The mucoadhesive systems are intended to extend the GRT by adhering them to the gastric mucous membrane. Bioadhesion on soft tissues of certain natural or synthetic polymers has been exploited to control as well as to prolong the gastric retention of the delivery systems.[43,44] The adhesion of the polymers with the mucous membrane may be mediated by hydration, bonding, or receptor mediated.[45] In hydration mediated adhesion, the hydrophilic polymers become sticky and mucoadhesive upon hydration. Bonding mediated adhesion may involve mechanical or chemical bonding. Chemical bonds may involve covalent or ionic bonds or Van der Waals forces between the polymer molecules and the mucous membrane. Receptor mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells. The polymers could be anionic or cationic or neutral. Table 2 is a brief description of the classification of these polymers.

Smart and Kellaway[46] reported prolonged gastric retention of dosage forms coated with Carbomer in mice. In vivo data of granules containing microcrystalline chitosan and furosemide showed higher AUC than that of the conventional dosage form.[47] Also, the granules exhibited slow release characteristic with a marked lag time. It appeared that due to its mucoadhesive properties, chitosan retained the drug in the

Table 2. Classification of bioadhesive polymers.

Anionic	Cationic	Neutral
Carboxymethylcellulose	Polylysine	Polyethylene glycol
Chondroitin sulfate	Polybrene	Polyevinyl pyrrolidone
Poly acrylic acid		Dextran
Pectin		
Carageenan		
Chitosan		
Alginic acid		

gastric mucosa for longer period of time. Although the in vivo data exhibited promising results for intragastric delivery, further characterization and evaluation of the system were necessary. Freeze-dried non-covalent polyionic complexes with porous structure based on polyacrylic acid and chitosan intended for delivering antibiotics to stomach have been developed by de la Torre.[48] The systems released about 70% of their contents in 2 hours.

Preda and Leucuta[49] developed a sustained release delivery system based on bioadhesive polymers: polyacrylic acid in gelatin microsphere. In vivo experiments with rat have shown significant retardation of gastric emptying of the beads due to adhesive characteristic of the gelatin/polyacrylic.

The exploitation of bioadhesive property of certain polymers on soft tissues in designing GRDS is unique. However, the inherent risk of this dosage form is the esophageal adherence resulting in drug-induced injuries.[50]

Swelling Systems

Swelling systems are also referred to as plug type systems. The presence of polymers in the systems promotes their swelling to a size that prevents their passage through pyloric sphincter resulting in prolonged GRT. However, a balance between the rate and extent of swelling and the rate of erosion of the polymer is crucial to achieve optimum benefits and to avoid unwanted side effects.

Agyilirah[51] developed a polymeric coating system that formed an outer membrane on the conventional tablets. In the dissolution media the membrane detached from the core and swelled to form a balloon that kept the unit floating. The size of the units increased by three to six folds. Thus, the floating ability as well as the increased dimension offered the system gastoretentive property.

High-Density Systems

High-density systems are intended to lodge in the rugae of the stomach withstanding the peristaltic movements. Systems with a density of 1.3 g/ml or higher are expected to be retained in the lower part of the stomach.[52]

The formulation of heavy pellets is based on the assumption that the pellets might be positioned in the lower part of the antrum because of their higher density. Devreux et al[53] reported that the pellets with density of at least 1.5 g/ml have significantly higher gastric residence time both in fasted and fed state. Clarke et al.[54] reported that the critical density to prolong gastric residence of pellets ranges between 2.4 to 2.8 g/ml. However, in vivo data do not confirm the effectiveness of this system,[55] as the primary determining factor of gastric emptying is the state of stomach when it is administered.

Floating Systems

The floating system is intended to float in and over the gastric contents resulting in prolonged GRT. Floating systems can be of effervescent or noneffervescent in nature. In the former ones gas generating excipients, e.g., bicarbonate salts and acidic ingredients are used that can form CO_2 in the presence of gastric acid. Also, volatile organic solvents have been introduced into the floating chamber to generate gas at physiological temperature. The trapped nascent gas inside the system keeps it floated. In noneffervescent systems, high level (about 75%) of highly swellable and gel forming excipients are used.

Sugito et al.[56] reported that the tablets with relative density of 0.86 g/ml exhibited longer gastric retention than tablets with relative density of 1.33 g/ml in non-fasting state. Various patents have been granted on different floating systems including capsules such as hydrodynamically balanced systems (HBS), tablets, and multiple-layered tablets.[57–59] In HBS, hydrocolloids are used to form a swelling-hydrated boundary layer in which air is trapped that offers the system its floating properties.

Systems with floatation chambers filled with gaseous materials,[60] or with inflatable chambers containing liquids that generate gas at body temperature[61] have been reported to remain afloated over gastric contents. Stockwell et al.[62] devised a system of alginate matrix capsule containing sodium bicarbonate that released carbon dioxide, which remained entrapped in the gel network. Ichikawa et al.[63] prepared a multiple-unit floating pill, which consisted of a core seed surrounded by two different layers. The primary layer contained sodium bicarbonate and tartaric acid, which generated carbon dioxide in aqueous media. The outer layer composed of a swellable membrane that trapped the gas resulting in floatation of the system. The system started floating within 10 minutes of immersion into the test media and remained floated over a period of 5 hours.

Matrix tablets containing hydroxypropyl methylcellulose, drugs, and gas generating agents have shown duration of floating over 8 hours with a floating lag time of half-hour.[64] Radiological studies suggested no adherence of the tablet to the gastric mucosa, and mean gastric residence time over 4 hours.

Oth et al.[65] developed a bilayer floating capsule using misoprostol as the model drug. The authors reported that the gastric residence times of more than 15 hours were achieved in fed state. Yang and Fassihi[66] developed a three-layered tablet. One of the outer layers contained gas-generating substance. The produced gas was trapped in a hydrated gel matrix. In vitro evaluation exhibited zero order release with maintaining buoyancy over 16 hours.

Kawashima et al.[67] developed hollow polymeric microspheres loaded with drug in their outer shells by emulsion-solvent diffusion methods. The system was reported to remain afloated over the surface of dissolution media for more than 12 hours. El-Gibaly[68] developed floating hollow microcapsules of chitosan by ionic interaction with a negatively charged surfactant. The system remained buoyant for over 12 hours in simulated gastric fluids and exhibited sustained drug release. Floating microparticles based on low density foam powder were developed by Streubel et al.[69]

Porous microparticles consisting of polypropylene foam powder, a drug, and polymers were prepared with an O/W solvent evaporation method. About 100% encapsulation efficiency was reported. However, the type of polymer used, the degree of drug load, and the nature of the drug significantly influenced the release kinetics of the microparticles.[70] ''Microbaloons,'' a hollow microsphere system for floating drug delivery system was developed by Sato et al.[71] It was prepared by the emulsion solvent diffusion method using enteric polymers and organic solvents. Employment of enteric polymers gave the system prolonged drug release characteristic. When administered with food, the in vivo studies exhibited prolonged gastric retention of the system.

Atyabi et al.[72] prepared coated ion-exchange resin beads as gastroretentive delivery systems. The resin had been charged with bicarbonate before it was coated with a semipermeable polymeric membrane of Eudragit-RS. In the presence of hydrochloric acid, bicarbonate was liberated, which formed carbon dioxide. The later was trapped inside the membrane resulting in floatation of the resin particle. Freeze dried oral dosage forms containing finely divided ion-exchange resins were developed by Burton et al.[73] The authors reported prolonged gastric residence and uniform distribution of the particles within the stomach.

Freeze dried sodium alginate beads had shown prolonged gastric residence times of more than 5.5 hours and the beads remained high up in stomach throughout the test period.[74] In 1 hour about 70% of the loaded drug, amoxicillin, was released from the beads, but incorporation of amylose moderately retarded the release rate.[75]

Cholestyramine, an anion exchange resin, exhibited mucoadhesive property to gastric mucosa.[76] Umamaheshwari et al.[77] took a combined approach of floating and bioadhesive techniques to develop a prolonged gastroretentive delivery system. They used ion-exchange resin particles loaded with bicarbonate and acetohydroxamic acid; the particles were then coated with cellulose acetate butyrate by emulsion solvent evaporation method. The system exhibited floating ability due to the carbon dioxide generation when the microgranules were exposed to gastric fluid. The mucoadhesiveness of the microparticles was studied by employing fluorescent probe.

Floating dosage forms have been proposed with the expectation that they will remain buoyant on the gastric contents due to their lower bulk density than that of the gastric contents at any time. In the fasting state, the stomach usually contains saliva, mucus, and cellular debris. Thus, it is expected that the floating systems will remain on top of the gastric contents at any time point. Nevertheless, the state of the stomach, i.e., fed or fasted state in relation to drug administration, plays a major role in the success of these systems. Due to unpredictable gastric emptying associated with migrating myoelectric complex (MMC) motility pattern, multiparticulate systems are more advantageous than the single unit systems, as the later ones experience ''all or none'' emptying pattern from the stomach.

Miscellaneous Systems

Groning and Heun[78] have proposed incorporation of triethanolamine myristate into the delivery system as a passage delaying agent. That was based on the fact that some of the fatty acids might reduce the gastric emptying rate via stimulation of fat receptors. However, the intersubject variability was very high with that delivery system.

Large single-unit dosage form that is above the size of the noncontracted pyloric sphincter opening was proposed by Cargill et al.[79,80] In vivo studies with that dosage form in beagle dogs showed positive results. In vivo evaluation of large dosage forms (greater than or equal to 2.5×2.5 cm) having rigid shell exhibited prolonged gastric retention.[81] Nevertheless, practical value of those devices was minimal due to the risk of gastric obstruction or permanent retention of the system.

Klausner et al.[82] developed highly rigid, unfolding polymeric membranes with extended dimensions intended for use in controlled release intragastric delivery of drugs. Membrane thickness significantly

influenced the release kinetics. In vivo evaluations were performed in dogs using x-ray to locate the delivery systems in the gastrointestinal tract. However, there are possibilities of the polymeric films to get stuck in the esophagus causing extreme discomfort to the patient or drug related injuries. In addition, repeated administration of such rigid systems may result in gastric obstruction.

CONCLUSIONS

To derive maximum therapeutic benefits from certain drug substances, it is desirable to prolong their gastric residence time. In addition, the delivery system should exhibit a burst followed by a sustained release of the active agent. Various techniques and approaches have been employed to develop GRDS. Development of such systems requires a thorough understanding of gastrointestinal physiology, and physicochemical properties of the drug substances. Floating, and bioadhesive systems appear to be the promising GRDS. Still the primary determining factor of gastric emptying is the presence of food. Nevertheless, there are opportunity and potential for development of effective gastroretentive delivery systems with the aim of improving bioavailability of the drugs that exhibit absorption window in the proximal and/or mid gastrointestinal tract.

REFERENCES

1. Rouge, N.; Buri, P.; Doelker, E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int. J. Pharm. **1996**, *136*, 117–139.
2. Fell, J.T.; Whitehead, L.; Collet, H. Prolonged gastric retention using floating dosage forms. Pharm. Technol. **2000**, *24* (3), 82–90.
3. Matharu, R.S.; Sanghavi, N.M. Novel drug delivery system for captopril. Drug Dev. Ind. Pharm. **1992**, *18*, 1567–1574.
4. Fell, J.T. Delivery systems for targeting to specific sites in the gastrointestinal tract. J. Pharm. Pharmacol. **1999**, *51* (Suppl), 41.
5. Baumgartner, S.; Kristl, J.; Vrecer, F.; Vodopivec, P.; Zorko, B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int. J. Pharm. **2000**, *195* (1–2), 125–135.
6. Deshpande, A.A.; Rhodes, C.T.; Shah, N.H.; Malick, A.W. Controlled-release drug delivery systems for prolonged gastric residence: an overview. Drug Dev. Ind. Pharm. **1996**, *22* (6), 531–539.
7. Ateshkadi, A.; Lam, N.; Johnson, C.A. Clin. Pharm. **1993**, *12*, 34–48.
8. Chatterjee, A.; Yasmin, T.; Bagchi, D.; Stohs, S.J. The bactericidal effects of lactobacillus acidophilus, garcinol, and protykin compared to clarithromycin on Helicobacter Pylori. Mol. Cell. Biochem. **2003**, *243* (1–2), 29–35.
9. Menon, A.; Wolfgang, A.; Ritschel, A.; Sakr, A. Development of and evaluation of a monolithic floating dosage form for furosemide. J. Pharm. Sci. **1994**, *83*, 239–245.
10. Rubinstein, A. Microbially controlled drug delivery to the colon. Biopharm. Drug Dispos. **1990**, *11*, 465–475.
11. Dressman, J.B.; Berardi, R.R.; Dermentzoglou, L.C.; Russell, T.L.; Schmaltz, S.P.; Barnett, J.L.; Jarvenpaa, K.M. Upper gastrointestinal (GI) pH in young, healthy men and women. Pharm. Res. **1990**, *7*, 756–761.
12. Russell, T.L.; Berardi, R.R.; Barnett, J.L.; Dermentzoglou, L.C.; Jarvenpaa, K.M.; Schmaltz, S.P.; Dressman, J.B. Upper gastrointestinal pH in seventy-nine healthy, elderly, North American men and women. Pharm. Res. **1993**, *10* (2), 187–196.
13. Lui, C.Y.; Amidon, G.L.; Berardi, R.R.; Fleisher, D.; Youngberg, C.; Dressman, J.B. Comparison of gastrointestinal pH in dog and humans: implications on the use of the beagle dog as a model for oral absorption in humans. J. Pharm. Sci. **1986**, *75*, 271–274.
14. Mojaverian, P.; Chan, K.K.H. (a). Radiotelemetric determination of gastrointestinal pH, in vitro accuracy and in vivo reproducibility in man. Pharm. Res. **1988**, *5*, S-243.
15. Feldman, M.; Barnett, C. Dig. Dis. Sci. **1991**, *36*, 866–869.
16. Charman, W.N.; Porter, J.H.; Mithani, S.; Dressman, J.B. Physicochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. J. Pharm. Sci. **1997**, *86* (3), 269–282.
17. Varis, K.; IHamaki, T.; Harkonen, M.; Samlof, I.M.; Siruala, M. Gastric morphology, function, and immunology in first-degree relatives of probands with pernicious anemia and controls. Scand. J. Gastroenterol. **1979**, *14* (2), 129–139.
18. Holt, P.R.; Rosenberg, H.; Russell, R.M. Causes and consequences of hypochlorhydria in elderly. Dig. Dis. Sci. **1989**, *34* (6), 933–937.
19. Lake-Bakaar, G.; Quadros, E.; Beidas, S.; Elaskr,

M.; Tom, W.; Wilson, D.; Dinscoy, H.P.; Cohen, P.; Straus, E.W. Ann. Intern. Med. **1988**, *112*, 502–504.
20. Benn, A.; Cooke, W.T. Intraluminal pH of duodenum and jejunum in fasting subjects with normal and abnormal gastric or pancreatic function. Scand. J. Gastroenterol. **1971**, *6*, 313–317.
21. Mojaverian, P.; Chan, K.K.H.; Desai, A.; John, V. Gatrointestinal transit of a solid indigestible capsule as measured by radiotelemetry and dual gama scintigraphy. Pharm. Res. **1989**, *6*, 719–724.
22. Evans, D.F.; Pye, G.; Bramley, R.; Clark, A.G.; Dyson, T.J.; Hardcastle, J.D. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut **1988**, *29*, 1035–1041.
23. Fell, J.T. Targeting of drugs and delivery systems to specific sites in the gastrointestinal tract. J. Anat. **1996**, *189*, 517–519.
24. Sarna, S.K. Cyclic motor activity: migrating motor complex. Gastroenterology **1985**, *89*, 894–913.
25. Rubinstein, A.; Li, V.H.K.; Robinson, J.R. Gastrointestinal-physiological variables affecting performance of oral sustained release dosage forms. In *Oral Sustained Release Formulations: Design and Evaluation*; Yacobi, A., Halperin, W.E., Eds.; New York, Pergamon, 1988, (Chapter 6).
26. Schemann, M.; Ehlein, H.J. Mechanical characterstics of phase II and phase II of the interdigestive migrating motor complex in dogs. Gastroenterology **1986**, *91*, 117–123.
27. Wilding, I.R.; Coupe, A.J.; Davis, S.S. The role of γ-scintigraphy in oral drug delivery. Adv. Drug Deliv. Rev. **1991**, *7*, 87–117.
28. Shargel, L.; Yu, A. *Applied Biopharmaceutics and Pharmacokinetics*, 4th Ed.; Appleton and Lange: Philadelphia, 1999.
29. Hofmann, A.F.; Pressman, J.H.; Code, C.F.; Witztum, K.F. Controlled entry of orally administered drugs: physiological considerations. Drug Dev. Ind. Pharm. **1983**, *9* (7), 1077–1109.
30. Kutchai, H.C. The gastrointestinal system. In *Principles of Physiology*; 2nd Ed.; Berne, R.M., Levy, M.N., Eds.; Mosby Year Book: St. Louis, MO, 1996; 652–686.
31. Haus, L.C.; Fell, J.T. Effect of stress on the gastric emptying of capsules. J. Clin. Hosp. Pharm. **1984**, *9*, 249–251.
32. Reddy, S.M.; Sinha, V.R.; Reddy, D.S. Novel oral colon-specific drug delivery systems for pharmacotherapy of peptide and nonpeptide drugs. Drugs Today **1999**, *35* (7), 537–580.
33. Ollerenshaw, K.J.; Norman, S.; Wilson, C.G.; Hardy, J.G. Exercise and small intestinal transit. Nucl. Med. Commun. **1987**, *8*, 105–110.
34. Mojaverian, P.; Vlasses, P.H.; Kellner, P.E.; Rocci, M.L. Effects of gender, posture, and age on gastric residence time of an indigestible solid: Pharmaceutical considerations. Pharm. Res. **1988**, *5* (10), 639–643.
35. Kinget, R.; Kalala, W.; Vervoort, L.; Mooter, G.V. Colonic drug targeting. J. Drug Target. **1998**, *6* (2), 129–149.
36. Davis, S.S.; Khosla, R.; Wilson, C.G.; Washington, N. The gastrointestinal transit of a controlled release pellet formulation of tiaprofenic acid. Int. J. Pharm. **1987**, *35*, 253–258.
37. Park, H.M.; Chernish, J.M.; Rosenbeck, B.D.; Brunelle, R.L.; Hargrove, B.; Wellman, H.N. Gastric emptying of enteric coated tablets. Dig. Dis. Sci. **1984**, *29*, 207–212.
38. Coupe, A.J.; Davis, S.S.; Wilding, I.R. Variation in gastrointestinal transit of pharmaceutical dosage forms in healthy subjects. Pharm. Res. **1991**, *8* (3), 360–364.
39. Khosla, R.; Feely, L.C.; Davis, S.S. Gastrointestinal transit of non-disintegrating tablets in fed subjects. Int. J. Pharm. **1989**, *53*, 107–117.
40. Davis, S.S.; Hardy, G.J.; Taylor, M.J.; Whalley, D.R.; Wilson, C.G. The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). Int. J. Pharm. **1984**, *21*, 331–340.
41. Hunter, E.; Fell, J.T.; Sharma, H. The gastric emptying of pellets contained in hard gelatin capsules. Drug Dev. Ind. Pharm. **1982**, *8*, 751–757.
42. Marvola, M.; Aito, H.; Ponto, P.; Kanniksoki, A.; Nykanen, S.; Kokkonen, P. Gastrointestinal transit and concomitant absorption of verapamil from single unit sustained released tablet. Drug Dev. Ind. Pharm. **1987**, *13*, 1593–1609.
43. Ch'ng, H.S.; Park, H.; Kelly, P.; Robinson, J.R. Bioadhesive polymers as platforms for oral controlled drug delivery. II. Synthesis and evaluation of some swelling, water insoluble polymers. J. Pharm. Sci. **1985**, *74* (4), 399–405.
44. Longer, M.A.; Ch'ng, H.S.; Robinson, J.R. Bioadhesive polymers as platforms for oral controlled drug delivery. III. Oral delivery of Chlorothiazide using bioadhesive polymers. J. Phar. Sci. **1985**, *74* (4), 406–411.
45. Park, K.; Robinson, J. Bioadhesive polymers as platform for oral-controlled drug delivery: method to study bioadhesion. Int. J. Pharm. **1984**, *19* (1), 107–127.
46. Smart, J.D.; Kellaway, I.W. Pharmaceutical factors

influencing the rate of gastrointestinal transit in an animal model. Intl. J. Pharm. **1989**, *53*, 79–83.
47. Sakkinen, M.; Linna, A.; Ojala, S.; Jurjenson, H.; Veski, P.; Marvola, M. In vivo evaluation of matrix granules containing microcrystalline chitosan as a gel forming excipient. Int. J. Pharm. **2003**, *250* (1), 227–237.
48. De la torro, P.M.; Torrado, S.; Torrado, S. Interpolymer complexes of poly(acrylic acid) and chitosan: influence of the ionic hydrogel-forming medium. Biomaterials **2003**, *24* (8), 1459–1468.
49. Preda, M.; Leucuta, S.E. Oxprenolol-loaded bioadhesive microspheres: preparation and in vitro/in vivo characterization. J. Microencapsul **2003**, *20* (6), 777–789.
50. Kikendall, J.W.; Friedman, A.C.; Oyewole, M.A.; Fleischer, D.; Johnson, L.F. Pill-induced esophageal injury. Case reports and review of the medical literature. Dig. Dis. Sci. **1983**, *28*, 174–182.
51. Agyilirah, G.A.; Green, M.; duCret, R. Evaluation of gastric retention properties of a cross-linked polymer-coated tablet versus those of a nondisintegrating tablet. Int. J. Pharm. **1991**, *75*, 241–247.
52. Bechgaard, H.; Baggesen, S. Propoxyphene and norpropoxyphene: influence of type of controlled release formulation on intra-and inter-subject variations. J. Pharm. Sci. **1980**, *69* (11), 1327–1330.
53. Devereux, J.E.; Newton, J.M.; Short, M.B. The influence of density on the gastrointestinal transit of pellets. J. Pharm. Pharmacol. **1990**, *42*, 500–501.
54. Clarke, G.M.; Newton, J.M.; Short, M.B. Comparative gastrointestinal transit of pellet systems of varying desnsity. Int. J. Pharm. **1995**, *114* (1), 1–11.
55. Davis, S.S.; Stockwell, A.F.; Taylor, M.J.; Hardy, J.G.; Whalley, D.R.; Wilson, C.G.; Bechgaard, H.F.N. Christensen, the effect of density on the gastric emptying of single-and multiple-unit dosage forms. Pharm. Res. **1986**, *3* (4), 208.
56. Sugito, K.; Ogata, H.; Goto, H.; Noguchi, M.; Kogure, T.; Takano, M.; Maruyama, Y.; Sasaki, Y. Gastrointestinal transit of non-disintegrating silid formulations in humans. Int. J. Pharm. **1990**, *60*, 89–97.
57. Seth, P.R.; Tossounian, J.L. Sustained Release Pharmaceutical Capsules. US Patent 4,126,672, November 1978.
58. Seth, P.R.; Tossounian, J.L. Novel Sustained Release Tablet Formulations. US Patent 4,167,558, September 1979.
59. Watanabe, S. Kayano, M. Ishino, Y. Miyao, K. Solid Therapeutic Preparation Remaining in the Stomach. US Patent 3,976,764, August 1976.
60. Harrigan, R.M. Drug Delivery Device for Preventing Contact of Undissoved Drug with the Stomach Lining. US Patent 4,055,178, October 1977.
61. Michaels, A.S.; Bashaw, J.D.; Zaffaroni, A. Gastro-Inflatable Drug Delivery Device. US Patent 3,901,232, 1975.
62. Stockwell, A.F.; Davis, S.S.; Walker, S.E. In vitro evaluation of alginate gel systems as sustained release drug delivery systems. J. Control. Release **1986**, *3*, 167–175.
63. Ichikawa, M.; Watanabe, S.; Miyake, Y. A new multiple-unit oral floating dosage system. I. Preparation and in vitro evaluation of floating and sustained release characteristics. J. Pharm. Sci. **1991**, *80*, 1062–1066.
64. Baumgartner, S.; Kristl, J.; Vrecer, F.; Vodopivec, P.; Zorko, B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int. J. Pharm. **2000**, *195* (1–2), 125–135.
65. Oth, M.; Franz, M.; Timmermans, J.; Moes, A. The bilayer floating capsule: a stomach-directed drug delivery system for Misoprostol. Pharm. Res. **1992**, *9* (3), 298–302.
66. Young, L.; Fassihi, R. Zero-order release kinetics from a self correctable floatable asymmetric configuration drug delivery system. J. Pharm. Sci. **1996**, *85*, 170–173.
67. Kawashima, Y.; Niwa, T.; Takechi, H.; Hino, T.; Itoth, Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J. Pharm. Sci. **1992**, *81*, 135–140.
68. El-Gibaly, I. Development and in vitro evaluation of novel floating chitosan microcapsules for oral use: comparison with non-floating chitosan microspheres. Int. J. Pharm. **2002**, *249* (1), 7–21.
69. Streubel, A.; Siepmann, J.; Bodmeier, R. Floating microparticles based on low density foam powder. Int. J. Pharm. **2002**, *241* (2), 279–292.
70. Struebel, A.; Siepmann, J.; Bodmeier, R. Multiple units gastroretentive drug delivery systems: a new preparation method for low density microparticles. J. Microencapsul. **2003**, *20* (3), 329–347.
71. Sato, Y.; Kawashima, Y.; Takeuchi, H.; Yamamoto, H. In vivo evaluation of riboflavin-containing microbaloons for floating controlled drug delivery system in healthy human volunteers. J. Control. Release **2003**, *93* (1), 39–47.
72. Atyabi, F.H.L.; Sharma, H.A.H.; Mohammed, T.J.

Fell, in vivo evaluation of novel gastric retentive formulation based on ion-exchange resins. J. Control. Release **1996**, *42* (2), 105–113.
73. Burton, S.; Washington, N.; Steele, R.J.C.; Musson, R.; Feely, L. Intragastric distribution of ion-exchange resins: a drug delivery system for the topical treatment of the gastric mucosa. J. Pharm. Pharmacol. **1995**, *47* (11), 901–906.
74. Whitehead, L.; Fell, J.T.; Collett, J.H.; Sharma, H.L.; Smith, A.M. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. J. Control. Release **1998**, *55* (1), 3–12.
75. Whitehead, L.; Collett, J.H.; Fell, J.T. Amoxicillin release from a floating dosage form based on alginates. Int. J. Pharm. **2000**, *210*, 45–49.
76. Jackson, S.J.; Perkins, A.C. In vitro assessment of the mucoadhesion of cholestyramine to procine and human gastric mucosa. Eur. J. Pharm. Biopharm. **2001**, *52* (2), 121–127.
77. Umamaheshwari, R.B.; Jain, S.; Jain, N.K. A new approach in gastroretentive drug delivery system using cholestyramine. Drug Deliv. **2003**, *10* (3), 151–160.
78. Groning, R.; Heun, C. Oral dosage forms with controlled gastrointestinal transit. Drug Dev. Ind. Pharm. **1984**, *10* (4), 527–539.
79. Cargill, R.I.; Caldwell, J.; Engle, K.J.; Fix, A.; Porter, P.A.; Gardner, C.R. Controlled gastric emptying. I. Effects of physical properties on gastric residence times of non-disintegrating geometric shapes in beagle dogs. Pharm. Res. **1988**, *5* (8), 533–536.
80. Cargill, R.; Engle, K.; Gardner, C.R.; Porter, P.; Sparer, R.V.; Fix, J.A. Controlled gastric emptying. II. In vitro erosion and gastric residence times of an erodible device in beagle dogs. Pharm. Res. **1989**, *6* (6), 506–509.
81. Klausner, E.A.; Lavy, E.; Stepensky, D.; Friedman, M.; Hoffman, A. Novel gastroretentive dosage forms: evaluation of gastroretentivity and its effect on riboflavin absorption in dogs. Pharm. Res. **2002**, *19* (10), 1516–1523.
82. Klausner, E.A.; Eyal, S.; Lavy, E.; Friedman, M.; Hoffman, A. Novel levodopa gastroretentive dosage form: in vivo evaluation in dogs. J. Control. Release **2003**, *88* (1), 117–126.