

FORMULATION TECHNOLOGIES FOR DRUG DELIVERY TO THE UPPER SMALL INTESTINAL WINDOW

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ABSTRACT

Oral bioavailability of certain drugs can be limited by the residence time of pharmaceutical formulation in the upper gastrointestinal tract. Gastric emptying plays an important role in the dynamics of drug absorption and can lead to variable and unpredictable availability. And it becomes more critical for drugs which are exclusively absorbed in the upper small intestine or in a limited segment of the intestine. To overcome this restriction and to increase the bioavailability of these drugs, controlled drug delivery systems with a prolonged residence time in the stomach can be used. Approaches to achieving prolonged residence times of the devices in the upper part of the gastrointestinal tract include the use of bioadhesive, size increasing, and floating drug delivery systems.

INTRODUCTION

Oral ingestion is the predominant and most preferable route for drug delivery. Importantly, it allows unassisted administration by the patient without the need for trained personnel (as this is the case with most parenterally administered dosage forms).

As the scientists acquire a better understanding of the physicochemical and biological parameters pertinent to oral drug delivery system performance these are becoming increasingly sophisticated. Despite tremendous advancements in drug delivery, time-controlled oral drug delivery systems offer several advantages over immediate-release dosage forms, including the minimization of fluctuations in drug concentrations in the plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic efficiencies and reduced side effects; a reduction of the total dose administered (while providing similar therapeutic effects); and a reduction of the administration frequency, leading to improved patient compliance. While, 'standard' controlled-release

dosage forms offer only limited advantage for drugs that have an absorption window in the upper small intestine e.g. levodopa [Erni W., 1987], furosemide [Ozdemir N., 2000] and riboflavin [Hoffman A., 2004]. In order to increase the bioavailability of this type of drug, the residence time of the controlled-release dosage forms in the upper gastrointestinal tract needs to be prolonged.

PHYSIOLOGY OF INTESTINAL TRACT:

The GI tract is essentially a tube about nine metres long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the GI tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents. Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH1–3) and air. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. The GI tract is in a state of continuous motility consisting of two modes: inter-digestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract. The inter-digestive motility pattern is commonly called the ‘migrating motor complex’ (‘MMC’) and is organized in cycles of activity and quiescence. Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases. In the inter-digestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90–120 minutes. A full cycle consists of four phases, beginning in the lower oesophageal sphincter/ gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum. Phase III is termed the ‘housekeeper wave’ as the powerful contractions in this phase tend to empty the stomach of its fasting contents and indigestible debris. The administration and subsequent ingestion of food rapidly interrupts the MMC cycle, and the digestive phase is allowed to take place. The upper part of the stomach stores the ingested

food initially, where it is compressed gradually by the phasic contractions. The digestive or fed state is observed in response to meal ingestion. It resembles the fasting Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the inter-digestive MMC. It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern and/or by the presence of food. The fasted-state emptying pattern is independent of the presence of any indigestible solids in the stomach. Patterns of contractions in the stomach occur such that solid food is reduced to particles of less than 1mm diameter that are emptied through the pylorus as a suspension. The duration of the contractions is dependent on the physiochemical characteristics of the ingested meal. Generally, a meal of ~450kcal will interrupt the fasted state motility for about three to four hours. It is reported that the antral contractions reduce the size of food particles to $\leq 1\text{mm}$ and propel the food through the pylorus. However, it has been shown that ingestible solids $\leq 7\text{mm}$ can empty from the fed stomach in humans.

REQUIREMENT FOR GASTRIC RETENTION:

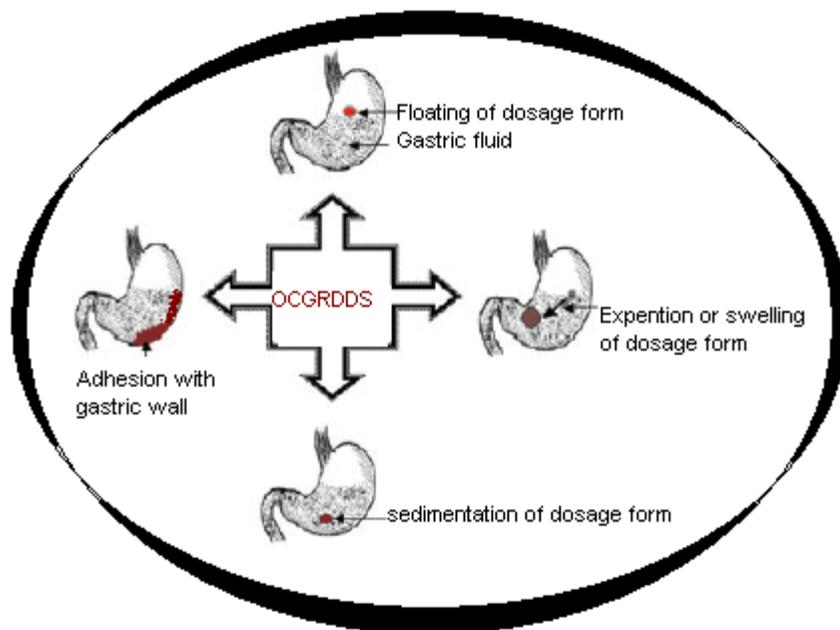
From the discussion of the physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

FACTORS AFFECTING GASTRIC RETENTION:

Gastric residence time of an oral dosage form is affected by several factors. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. (Wilson CG., 1989) The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce

sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state. The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time. Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down. (Singh BN., 2000) The resting volume of the stomach is 25 to 50 mL. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids. Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves.

Based upon physiology and factor effecting gastric emptying various approaches have been followed to encourage gastric retention of an oral dosage form and the main approaches to prolonging the gastric residence time of pharmaceutical dosage forms include bioadhesive delivery systems, which adhere to mucosal surfaces(Lee JW., 2000; Ch'ng H.S.,1985; Jimenez N R., 1993); devices that rapidly increase in size once they are in the stomach to retard the passage through the pylorus(Klausner E, 2003); and density-controlled delivery systems, which float on gastric fluids (Hwang SJ., 1998; Singh BN., 2000; Machida. Y., 1989; Bardonnnet PL., 2006; Streubel A., 2006



Types of Gastroretentive systems

Bioadhesive drug delivery systems

Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and extend the gastroretention time by increasing the intimacy and duration of contact between the dosage form and the biological membrane. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. The primary function of mucus is to protect the surface mucosal cells from acid and peptidases; also it helps as a lubricant for the passage of solids and as a barrier to antigens, bacteria, and viruses (Gupta P.K., 1992). The adherence of the delivery system to the gastric wall increases residence time of dosage form at a particular site and improve bioavailability, this binding of polymers to the mucin– epithelial surface can be subdivided into three broad categories: hydration-mediated adhesion, bonding-mediated adhesion, and receptor-mediated adhesion (Park K., 1984).

Hydration-mediated adhesion

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

Bonding-mediated adhesion

The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical–mechanical bonding and chemical bonding. Physical–mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive Vander Waals interactions and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups (Chien Y.W., 1992).

Receptor-mediated adhesion

Certain polymer binds to specific receptor sites on the surface of cells, and therefore enhances the gastric retention of dosage forms. Certain plant lectins like tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx. An unresolved issue related to bio/mucoadhesive systems is the attachment site of the system in the gut wall. The systems can attach both to the mucus layer and the epithelial surface of the stomach. In the former case, it is important to realize that the mucus layer in the stomach turns over continuously, and the mucus can be found not only on the surface of the lumen but also within the lumen (called the *soluble mucus*) (Lehr C.M., 2002). So, it is difficult to understand how mucoadhesive systems identify the designated attachment site. Bioadhesive polymers are classified on the basis of their charge. A few examples of bioadhesive polymers are listed in Table-1.

Akiyama *et al*, (1999), proposed the use of mucoadhesive microspheres consisting of a drug and Carbopol 934P (polyacrylic acid, polymerized in benzene and highly cross-linked with allyl sucrose), dispersed within a waxy matrix of polyglycerol esters of fatty acids. These systems adhered to the stomach mucosa in rats and Mongolian gerbils and thus prolonging the drug's gastrointestinal residence time after oral administration. The adherence can be attributed to the hydration and swelling of Carbopol in the microspheres upon contact with water. Importantly, parts of the macromolecules remain within the microspheres, whereas the rest is 'anchored' within the mucus layer.

The major challenge for bioadhesive drug delivery systems is the high turnover rate of the gastric mucus and the resulting limited retention times. Furthermore, specific targeting of the gastric mucus with bioadhesive polymers is difficult. Bioadhesive polymers (e.g. polycarbophil, Carbopol and chitosan) will stick to various other surfaces that they come into contact with (Khosla R., 1987; Sakkinen M., 2004). In addition, some time possible oesophageal binding of dosage form presents a challenge regarding safety aspects.

Table-1-Bioadhesive polymers

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

FLOATING DRUG DELIVERY SYSTEMS

Another promising approach is floating drug delivery systems these float immediately upon contact with gastric fluids for increasing the bioavailability of drugs with absorption windows in the upper small intestine. However, immediate floating can only be achieved if the density of the device is low at the very beginning. Devices with an initially high density (which decreases with time) first settle down in the stomach and, thus, undergo the risk of premature emptying. Inherent low density can also be provided eg. entrapment of air (e.g. hollow chambers [Krogel I., 1999]) or by the (additional) incorporation of low density materials (e.g. fatty substances or oils [Sriamornsak P., 2005], or foam powder [Streubel A., 2003 & 2002]).

Davis (1968) first described floating systems, these are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period .While the system floats over the gastric contents, the drug is released slowly at a desired rate (Mitra S.B., 1984), which results in increased gastroretention and reduction of fluctuation in plasma drug concentration (Fell J.T., 2000). Floating systems are classified as *effervescent* and *non-effervescent* systems.

Effervescent Floating Dosage Forms

Flotation of a drug delivery system in the stomach can be achieved by incorporating a floating chamber filled with vacuum, air, or an inert gas. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the CO₂ produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts (Sakr F.M., 1999). This CO₂ is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. These devices contain a hollow deformable unit that converts from a collapsed to an expanded position and returns to the collapsed position after a predetermined amount of time to permit the spontaneous ejection of the inflatable system from the stomach (Chawala *et al.*, 2003).

Ichikawa et al (Ichikawa M., 1991) developed a new multiple type of floating dosage system comprised of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37°C, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO₂ was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0g/mL. The system was having good floating ability independent of pH and viscosity while the drug (para-amino benzoic acid) released in a sustained manner.

Noneffervescent systems

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid and forming into tablets or capsules. Upon coming into contact with gastric fluid, these gel formers,

polysaccharides and polymers hydrate and form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the dosage form (Chawala *et al.*, 2003).

The following approaches used in designing intragastric floating systems (Bardonnet *et al.*, 2006).

Thanoo et al (Thanoo BC., 1993) developed polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated bio-fluids. Drug-loaded microspheres were able to float on gastric and intestinal fluids.

Whitehead et al (Whitehead L., 2000) prepared floating alginate beads incorporating amoxicillin. The beads were produced by drop-wise addition of alginate into calcium chloride solution, followed by removal of gel beads and freeze-drying. The beads containing the dissolved drug remained buoyant for 20 hours and high drug-loading levels were achieved.

Example of Drugs Formulated as Floating Drug Delivery Systems. (Single/Multiple Unit formulation)

Tablet	Capsule	Microsphere/Granules
Chlorpheniramine maleate (Deshpande A, 1997)	Nicardipine (Moursy N M, 2003)	Terfenadine (Jayanthi G, 1995)
Theophylline (Yang L, 1996)	Furosemide (Menon A, 1994)	Prednisolone (Inouye K, 1989)
Furosemide (Ozdemir N, 2000)	Misoprostal (Oth M, 1996)	Aspirin, griseofulvin (Thanoo B C, 1993)
Pentoxyfillin (Baumgartner S, 2000)	L- Dopa and benserazide (Erni W, 1987)	Ketoprofen (El-Kamel A H, 2001)
Ciprofolxacin (Talwar N, 2000)	Propranolol (Khattar D, 1990)	Iboprufen (Kawashima Y, 1991)
Atenolol (Rouge N, 1998)	Diazepam (Gustafson J H, 1981)	
Isosorbide di nitrate (Ichikawa M, 1991)		

The major drawback of low-density, floating drug delivery systems is their performance dependency upon the filling state of the stomach. However, this approach can successfully prolong the gastric retention time of drugs [Talukder R., 2004]

High-density systems

These systems, which have a density of $\sim 3 \text{ g/cm}^3$, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements (Devereux J.E., 1990). Such systems can be retained in the lower part of the stomach above a threshold density of 2.4–2.8 g/cm^3 , (Clarke G.M., 1995). Diluents such as barium sulphate (density = 4.9), zinc oxide and iron powder must be used to manufacture such high-density formulations.

The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm^3 .

Swelling and expanding systems

It is a promising approach for achieving gastroretention. Here after being swallowed, the dosage forms swell to a size that prevents their passage through the pylorus. As a result, the dosage form is retained in the stomach for a longer duration. These systems are sometimes referred to as *plug type systems* because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. These dosage forms must not swell or expand in the oesophagus or in the intestine if it is emptied prematurely from the stomach. The Gastroretentive dosage form will also need to display controlled release properties. The system should have sufficient rigidity to remain intact in the stomach and to withstand the mechanical forces in stomach. However it should decrease in size after it has performed its function and then transit through the intestine in the normal way. Various systems usually achieve increased size by expansion or swelling or through unfolding.

Expansion or swelling process either involve generation of gas in form of carbon dioxide, or use the properties of compressed porous material like hydrogels.

The swelling system composed with super-porous hydrogel have been investigated as Gastroretentive systems by Chen et al, (2000)

Klausner E. A., (2003) an Israeli worker developed an unfolding system comprising an inner polymeric and/or drug matrix layer with two shielding outer layer with a coat of microcrystalline cellulose to prevent adhesion.

The fasted stomach presents a challenge in terms of limited time available for increase in size and for retention to be achieved, while the lightly fed stomach provide sufficient residence time for a suitable size increase.

LIMITATIONS

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

CONCLUSIONS

A controlled drug delivery system with increased residence time in the stomach can be of great practical importance for drugs with an absorption window in the upper small intestine. Adequate control of the gastric residence time combined with time-controlled drug release patterns can significantly increase the bioavailability of the drug and, thus, the efficiency of the treatment. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing these techniques.

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