Enhanced Bioavailability via Extended Gastric Retention

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Abstract

The ability to prolong gastric residence times with the use of gastric retentive systems is particularly useful for drugs that act locally in the stomach and for those having site-specific absorptions in the upper intestine. Drugs entrapped into these dosage forms also display pharmacokinetic parameters that favor greater safety and efficacy. Many gastric retentive platforms have been studied and some have successfully been utilized in marketed drug products. There are typically three approaches that these platforms take to reside in the stomach longer. They alter the size, density, or adhesion of the delivery system in the gastric environment which leads to changes in drug liberation and absorption. This has a direct effect on the therapeutic effectiveness of the drug they are carrying. The development of these dosage forms is not however without its challenges and further research in this area is needed that shows true gastric retention has occurred. The purpose of this paper is to briefly describe gastric retention approaches and to highlight the enhanced bioavailability, safety, and other benefits of these formulations.

Keywords: Gastric retention; Oral controlled release; Drug delivery systems; Gastroretentive technologies

Introduction

Oral drug delivery is still the most widely used route of administration due to the ease of administration, better patient compliance, high acceptance by almost all age groups, and the manufacturing flexibility of preparing oral dosage forms. However, the oral route is not without its challenges. One major obstacle encountered is when drugs display variability in absorption throughout the gastrointestinal tract. In particular, those drugs having a small and specific site of absorption (narrow absorption window) in the upper intestine. This causes decreased bioavailability, and often more drugs are then needed to maintain therapeutic effectiveness due to not being fully absorbed.

Drugs having a specific segment of the intestine where they are recognized and preferentially absorbed is similar to our sense of taste and the specific area over which it is only sensed. For example, if we ingested a spoonful of sugar we would immediately detect a sense of sweetness as the sugar is recognized by specific taste receptors on our tongue. However, once we swallow and the sugar makes its way down the esophagus there is no more taste. Obviously, the sense of sweetness will only be noticed when the sugar is passing over the tongue receptors, and is irrespective of what happens further in the other parts of the gastrointestinal tract. We may cautiously say we have a "narrow window" for the four receptions of taste. Similarly, there are many pharmaceutical actives with narrow absorption windows [1] where they will predominantly be absorbed only in certain parts of the gastrointestinal tract (GIT), in particular the upper intestines. Once passed the limited area of narrow absorption, these drugs won't be readily bioavailable and therefore pharmacologically ineffective systemically due to the lack of sufficient absorption.

One can immediately prescribe that by extending the retention of these drugs in the gastric area and slowing release to maintain a constant stream of drug over the absorption window may enhance their bio-effectiveness. This area of research and the formulations having such properties are called extended gastric retention, or in short gastric retention. Particularly, this applies to the drugs with narrow absorption windows where the stomach acts as the port of delivery. Additionally, there are other occasions where retention of a pharmaceutical ingredient may be beneficial if retained in the gastric environment for extended periods. The treatment of gastric conditions such as treating gastric ulcers with antibiotics retained in the stomach is one such example [2]. For occasions when the active drug is unstable in the higher pH of the lower intestines and where absorption in the stomach or upper intestine would be preferred is another use of gastric retention technology, specifically for actives with no absorption preference. In all these occasions, the effectiveness and/or bioavailability of the active agent are achieved by retaining the drug in the stomach and preventing passage into the duodenum by normal physiological digestive processes. Therefore, the potential of the active ingredient to harm or otherwise effect the stomach lining, the possible production of degradation byproducts from acidic gastric juices, or the effect of other medical conditions such as diabetes that can affect gastric emptying should be considered for long-standing gastric retention delivery systems. This leads to the next question of how does one safely and effectively retains a drug in the stomach
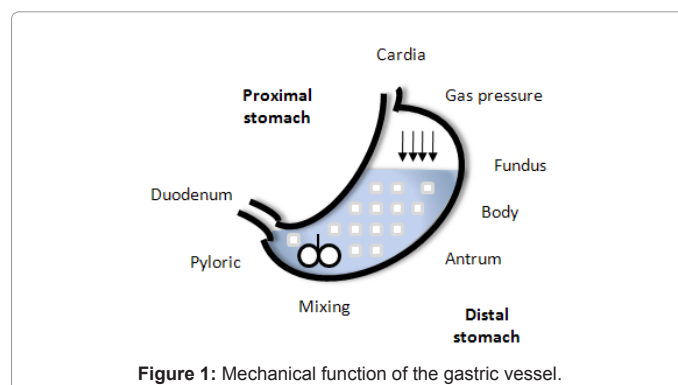

Figure 1: Mechanical function of the gastric vessel.

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Acyclovir	10-20% oral bioavailability; less bioavailability at higher doses; plasma peak about 2 hrs after dosing; no food effect on absorption; plasma elimination $t_{1/2}$ of about 2.5 hrs (in adults), 4 hrs (in neonates), 20 hrs (in anuric patients); non-metabolized drug elimination by renal excretion; 9-33% protein binding	[5,6]
Cefuroxime Axetil	The $t_{1/2}$ of 1.7hrs; 30-50% oral absorption; drug is hydrolyzed to cefuroxime with variable plasma concentration	[5,7]
Celecoxib	Unknown absolute bioavailability; peak plasma 2-4 hrs after dosing; extensive protein binding; mostly metabolized to carboxylic acid and glucoronide in the urine and feces; elimination $t_{1/2}$ of 11 hrs; plasma concentration of 40% (in patients with mild hepatic impairment, and 180% (in patients with moderate hepatic impairment which requires 50% reduced dose in such patients); predominantly metabolized by CYP2C9	[5]
Clarithromycin	Rapid oral absorption; 50-55% bioavailability (due to first-pass metabolism); plasma peak about 2 hrs after administration; 40-70% protein binding (concentration dependent); renal and non-renal elimination; several liver metabolites; oxidative N-demethylation and hydroxylation as primary metabolic pathway; elimination $t_{1/2}$ of 3-7 hrs (for the drug) and 5-9 hrs (for the primary metabolite, 14-hydroxylcalrithromycin); non-linear pharmacokinetics with longer $t_{1/2}$ for larger doses	[5]
Diltiazem HCl	Rapid oral absorption followed by reduced bioavailability due to first pass metabolism; the $t_{1/2}$ of 4 hrs [5] with 70-80% plasma protein binding	[8]
Furosemide	With 60% oral bioavailability and elimination $t_{1/2}$ of 1.5 hrs; about 65% of the drug excreted unchanged in urine with the rest conjugated to glucuronic acid in the kidney	[5]
Gabapentin	Oral absorption with no appreciable metabolism and no plasma protein binding; excreted unchanged mainly in the urine; the $t_{1/2}$ of about 6 hrs	[5]
Ibuprofen	Rapid oral absorption with high protein binding; undergoes hepatic metabolism with 90% of the drug metabolized to hydroxylate and carboxylate derivatives excreted by kidney; the $t_{1/2}$ of 2 hrs	[5]
Levodopa	Rapid absorption from the small bowel; plasma peak of 0.5-2 hrs after oral dosing; short plasma $t_{1/2}$ of 1-3 hrs; rate of gastric emptying, gastric pH, and the exposure to enzymes of the gastric and intestinal mucosa determine rate and extent of levodopa absorption	[5]
Metformin HCl	Primarily absorbed from small intestines; stable with no plasma protein binding; excreted unchanged in the urine; the $t_{1/2}$ of about 2 hrs; 50-60% bioavailability in fasted state; reduced and delayed absorption with food intake; plasma peak of 3 hrs after oral administration	[5,9]
Metoclopramide HCl	Rapid oral absorption; liver metabolism via sulfation and glucuronide conjugation; primary renal excretion; the t1/2 of 4-6hrs; plasma peak within 1 hr after oral dosing	[5]
Metoprolol Tartrate	Complete oral absorption with 40-50% oral bioavailability; the $t_{1/2}$ of 3-7 hrs with 12% plasma protein binding	[5]
Metronidazole	Rapid and complete oral absorption; the $t_{1/2}$ of 8 hrs with <20% binding to plasma proteins	[5]
Tetracycline	Variable and incomplete oral absorption; plasma peak at 2-4 hrs with t1/2 of 6-12 hrs; administered 2-4 times a day	[5]
Verapamil HCl	With 90% oral absorption; about 70% of the dose excreted as metabolites in urine and >16% in the feces with 3-4% of unchanged excreted drug; the $t_{1/2}$ of 2.8-7.4 hrs	[10]

Table 1: Pharmacokinetic Parameters of Gastric Retention Drug Candidates.

using gastric retention technology. For the drug or delivery system to first be retained in the stomach, it has to overcome one of the biggest obstacles for gastric retention, this being the mechanical movements of gastric emptying.

In the stomach a drug delivery system will be subjected to a dynamic wave of forces (expansion and contraction, mixing, grinding, and finally emptying) which it must resist. Looking at the stomach physiology (Figure 1), a number of other structural and anatomical features also affect the ability to be retained in the stomach. Furthermore, the gastric medium is always experiencing a wide range of foods and beverages with different calories, fat, and carbohydrate content, along with varying ranges of pH (acidic, neutral, slightly alkaline) and temperatures. Regional differences (cold or warm climates) in food and drink habits can drastically be different as well. Besides the state of stomach intake contents (solid, liquid, gas) and stomach forces, age, gender, and activity level are among other factors which affect the travel of the drug into and out of the gastric window. To make matters even more difficult, the inter- and intra-subject variability of these factors can vary widely at times. Further details regarding biopharmaceutics aspects of the gastric emptying process can be found in other references [3].

Drug Candidates for Gastric Retention

Drug candidates for gastric retention can include those for urinary infections (acetohydroxamic acid), viral infections (acyclovir), antibiotics (cefuroxime axetil, ciprofloxacin, clarithromycin, tetracycline, ofloxacin), calcium channel blockers (diltiazem HCl, verapamil HCl), diuretics (furosemide), non-steroidal anti-inflammatories (celecoxib, ibuprofen), those intended for type 2 diabetes (repaglinide, metformin HCl), Parkinson's disease

(levodopa), those to treat stomach and intestinal ulcers (ranitidine HCl, famotidine), and analgesics [4]. Relevant pharmacokinetics features of selected drug candidates can be found in Table 1, [5-10].

Drugs carried by gastric retentive systems display different pharmacokinetic parameters compared to traditional oral formulations. For example, the oral formulation of Madopar HBS® differs from conventional tablets as the actives are released slowly, increasing bioavailability by almost 60% and extending the time to reach C_{max} and half-life [11]. In the case of verapamil floating pellets, enhanced bioavailability and gastric retention were seen over a conventional tablet with higher t_{max} (3.75 hr versus 1.21 hr) and AUC values (364.65 ng.h.ml^{-1} versus 224.22 ng.h.ml^{-1}) for the gastric retentive pellets [12]. In the classic LADME (liberation, absorption, distribution, metabolism, elimination) process for drug disposition in the body, we can see that gastric retentive systems have the most effect on the liberation and absorption stages. The changes to the way drug is released and its movement into the systemic circulation caused by these dosage forms have many favorable benefits that are directly related to their different pharmacokinetic behaviors. A list of some important benefits gastric retentive systems have over traditional oral formulations is shown in Table 2 [13-15].

Approaches to Gastric Retention

The gastric compartment, as seen in Figure 1, has simply an inlet (cardiac) and an outlet (pylorus). Once a drug or drug delivery platform is orally administered, it can travel between these two points in several different paths and speeds. The longer it takes to move from the entry of the stomach to the entry of the duodenum, the greater the gastric retention time (Figure 1).
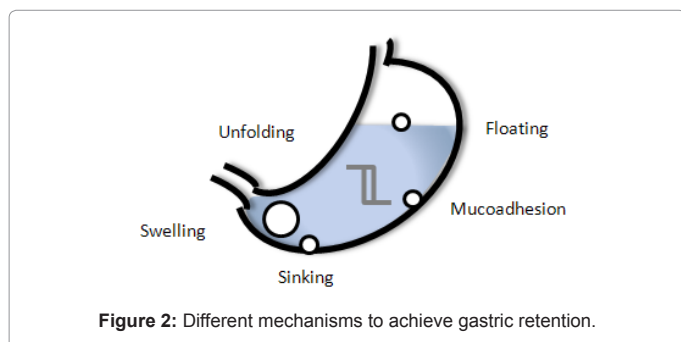
Figure 2: Different mechanisms to achieve gastric retention.

Parameter	Conventional dosage form	GRDDS
Toxicity	Higher toxicity risk	Lower toxicity risk
Patient compliance	Lower level	Higher level
Dose dumping	Lower risk of dose dumping	Higher risk of dose dumping if technology fails
Adverse effects	Higher chances	Chances are reduced due to fewer blood level peaks outside therapeutic range
Overall health care cost	May be higher	In spite of higher initial cost, overall treatment cost may be less due to improved therapeutic benefit, fewer side effects, reduced time for health care personnel to dispense and administer drugs and monitor patients

*Gastro retentive drug delivery systems (GRDDS)

Table 2: Comparison of GRDDS* and conventional oral dosage forms [13-15].

Is it then possible to achieve gastric retention in a natural way? The answer is yes, since gastric retention is decided by the gastric emptying process. We know, for example, that solids travel slower than liquids, and hence are associated with a slower gastric emptying cycle. Therefore the more solid the nature of the stomach contents, the longer the gastric retention. This is where the effect of fed or fasted state plays an important role. There is no doubt that drug will stay longer in the gastric compartment if mixed with solids, in other words, a fed state stomach. This therefore is a natural way to provide extended gastric retention, compared to an empty stomach or stomach filled by liquids. The nature of the solid can also play an important role as indigestible solids retain their solid nature for longer time periods versus digestible solids. Another natural way to alter gastric retention is by the total fat content (or the calorie content) of ingested foods. High calorie content food can provide longer gastric retention than a lower calorie food source. Patients having disorders such as gastroparesis that naturally delay gastric emptying can also be considered a natural occurrence that leads to greater gastric retention times. In the above mentioned natural examples, it is important to note that gastric retention of a drug will be achieved regardless of the type of oral dosage form administered; e.g., granules, powders, or immediate release tablets all will have enhanced retention. However, to take full advantage of drug gastric retention capabilities, non-natural approaches of carefully-designed dosage forms are needed.

There are in fact three general mechanisms by which we can extend gastric retention by non-natural ways. We can 1) manipulate the size of the dosage form after ingestion such that it becomes large enough to not pass the pylorus. Depending on the stomach content, we can 2) manipulate the density of the dosage form such that it becomes buoyant and floats over the surface of the gastric content or oppositely sinks to the bottom of the gastric contents. Lastly, we can have 3)

enhanced interaction between the dosage form and the stomach lining via adhesion mechanisms. Therefore, the concepts behind these primary approaches of gastric retention drug delivery platforms fall into the three main categories of size, density, and bioadhesiveness as described in the next section and shown in Figure 2.

Size

The process of size enlargement can occur when the dosage form contacts the gastric juices and swells such that its size or shape prevents easy passage through the pyloric sphincter and into the duodenum. Size-dependent approaches can be classified as either unfolding or swelling type platforms. With unfolding platforms, the dosage form is physically squeezed into a small size before administration, and becomes unfolded when contacted with the gastric medium. Although numerous designs have been proposed for expandable systems [16,17], biodegradable polymers in compressed form are the prime choice. Nevertheless, gastroretentive products functioning based on unfolding mechanisms are not commercially available. With swelling type platforms, the dosage form grows in size when in contact with the gastric medium due to intermolecular forces of hydrogen bonding, electrostatic, osmotic, and van der Waals interactions. This requires the dosage form to include excipients having characteristics that favor theses attractive forces. Technologies examined or developed based on the swelling mechanism primarily utilize hydrogel systems where extensive hydrogen bonding is provided by high molecular weight hydrophilic polymers in contact with water. The most common example is the use of high molecular weight hydroxypropyl methylcellulose or polyethylene oxide alone or in the combination. One can conceive that these hydrogel systems, in their swollen state, cannot provide sufficient strength to the dosage form to resist all the mechanical gastric forces we described earlier. They easily erode due to the lack of chemical crosslinking in their structures (Figure 3). These dosage forms thus provide little if any gastric retention in the fasted state. They typically have to be administered with medium to high calorie food in order to achieve effective retention times. Increasing the mechanical strength of these hydrogel systems with the addition of a crosslinker can generate another class of gastroretentive platforms having good swelling capacity while maintaining physical integrity in the swollen state. Moreover, the addition of pores into a chemically crosslinked hydrogel system can provide faster swelling kinetics and a more favorable system due to the rapid swelling occurring before they can be emptied from the stomach. For over a decade or so, researchers have developed different generations of superporous hydrogels, conventional, composite and hybrids, to meet both the swelling and strength requirements for these gastroretentive systems [18-23] (Figure 3).

Density

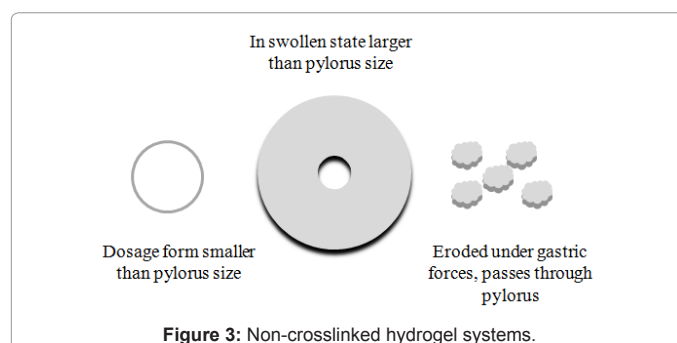Specific dosage forms can use the presence of a liquid in the

Figure 3: Non-crosslinked hydrogel systems.

stomach to effectively enhance gastric retention. The idea is to stop the movement of the dosage form in the current of the gastric contents by forcing them to float over the surface or sink to the bottom of the liquid in the gastric vessel. To achieve this goal, these dosage forms include gases, light oils, and light plastics or heavy inorganic compounds into the dosage form.

Classified as non-effervescent or effervescent, the former utilize high amounts of gel-forming polymers such as hydroxypropyl methylcellulose, sodium carboxymethylcellulose, sodium alginate and similar [24]. These polymers are mixed with the drug and encapsulated within a gelatin capsule. When taken orally, the polymer swells in the gastric medium providing an erodible outer layer from which drug is released in a controlled manner. This technology is very similar to the one discussed on swelling systems based on non-crosslinked hydrogel polymers. To improve buoyancy and drug release, many technologies have been studied, these include bilayers where one layer is responsible for buoyancy and the other for drug release [16], a multilayer laminate that can float [17], platforms with microporous compartment [21], bilayer system containing hollow polystyrene sphere [25] and a coated bioadhesive floating system [26]. On the other hand, effervescent systems function by entrapping gas within their structure that is generated most often from the reaction between an organic/gastric acid and a carbonate [1], citric acid and sodium bicarbonate for instance. All these platforms can be administered as a single or multiple units; however multiple units display a greater survival rate with longer than 3 hours of gastric retention as confirmed by X-ray photography and gamma-scintigraphy.

High density systems (about 2.5 gcm^{-3}) tend to sink to the bottom of the stomach and become entrapped within the folds of the antrumn where they can withstand peristaltic waves. High density systems have been tested in ruminants, but have never been examined in human and hence there is no commercially available product [24,27,28].

Bioadhesiveness

If the dosage form favorably interacts with the stomach lining (bioadhesive), it can potentially provide greater gastric retention. Bioadhesive systems can stay longer in the stomach by binding themselves to the gastric epithelial cell of the stomach wall [25]. Polyacrylic acid, chitosan, dextran, sodium alginate, cholestyramine, hydroxypropyl methylcellulose and many others have been studied for their bioadhesive ability to prolong gastric retention. Factors such as the rapid turnover of the stomach mucus layer, the presence of water (highly hydrated condition of the stomach) and swelling of such polymers in this aqueous environment can decrease the efficiency of bioadhesive systems.

Other approaches: Magnetic systems are comprised of an internal magnetic material in the dosage form and an external magnet that is placed externally on the abdomen. These systems have shown excellent bioavailability results in dogs and rats [26,29], however efficacy in human has yet to be proven due to patient incompliance and inaccurate positioning of the external magnet [29].

Challenges

A number of challenges have plagued gastric retention systems since their inception. Some of these major factors are discussed below.

Extent of retention

What is the number of hours of retention that one can claim, upon which, gastric retention is said to be achieved? Is 2 hrs, 4 hrs, or 8 hrs sufficient, and did it occur in the fasted state, in fed state, and with a low or high calorie food?

Since in the fed state of the stomach, the pylorus is closed, most of these technologies if taken with food may display some sort of success due to natural extended retention of the stomach contents in the fed state. However, retention of an object during the fasted state of the stomach where human pylorus remains open is quite challenging. The human pylorus has a diameter of about 12 ± 7 mm and therefore any object with a size range of about 5-10 mm can easily be moved out of the stomach during the fasted state where the pylorus is open. Given the fact that gastric motility is at its strongest pace when the stomach is empty, a gastric retention platform as large as 15 mm will likely be the minimum size which might resist emptying and provide drug retention in the stomach.

Proof of retention

Does it work *in vitro* and *in vivo*? After a formula concept for a potential gastroretentive platform is identified and developed, it has to eventually go through proof of principal studies. In order to perform proof of principal studies in vitro, a device that can exactly mimic the stomach conditions in both fasted and fed states is needed. For pre-clinical studies, the right animal model must be chosen to shown safety as well as feasibility of the dosage form before human trial can begin. Since current science lacks both reliable in-vitro trials and comparable animal models one is left to rely on only clinical experiment trials. Before being examined in human subjects, it is necessary that the selected formula be proven to be non-toxic and safe for human administration.

Product stability

What is the identity, potency and purity of a gastroretentive system? How do we define stability of a gastroretentive technology or system? Like a pharmaceutical active, we need to prove that the gastroretentive technology incorporated into the dosage form works all the time. We need to verify it's pure, potent; its identity doesn't change over time or under certain circumstances. For all this to be verified and identified there needs to be many established and validated analytical techniques in place. When evaluating drug stability during the pre-formulation stage of the drug development, one may consider one, two or three factors under which drug purity, potency and identity may change. There will be much effort to establish drug stability under defined conditions (temperature, relative humidity, UV light for instance). Given all the factors that might affect gastric retention to a greater or a lesser extent, one can conclude that there will be no simple solution to establish and study gastric retention of an active [4].

Conclusion

Some have said that gastric retention is the "Holy Grail" in oral drug delivery. The ability to enhance bioavailability for drugs having poor absorption over the entire gastrointestinal tract, decrease adverse effects, lower drug loads, and the convenience of less daily dosing are most likely the reasons for this statement. However, to develop an effective gastric retentive delivery system numerous factors need to considered. First, the drug and the dosage form itself must be safe to swallow and also not to cause harm when retained in the stomach for extended periods. Second, the way the drug is taken with regards to meals and drink need to be established to minimize variability. And last, the dosage form without harm must leave the gastric environment and enter the intestines at a specific time to be

safety eliminated. Because of these challenges there still is much needed research and development that needs to be done to further these delivery systems before they become substantially significant an economical in clinical practice.

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