ADVANCEMENTS IN CONTROLLED RELEASE GASTRORETENTIVE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT:
Oral delivery of the drug is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulations but has a drawback of non-site specificity and short gastric resident time. In order to overcome the drawbacks of conventional oral drug delivery systems, several technical advancements have led to the development of gastro retentive drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention. Afterwards, we have reviewed various gastroretentive approaches designed and developed until now, i.e. floating drug delivery system (FDDS), bio- or mucosahesive system, expandable, unfoldable system, high density system, raft forming system, super porous hydrogel system and magnetic systems. Among these systems, FDDS have been most commonly used. Finally, advantages, disadvantages, evaluation, marketed preparation and future potential of gastro retentive drug delivery systems were covered.

KEY WORDS: Gastroretentive drug delivery system, Gastric retention time, Gastric emptying time, Floating system, Migrating myloelectric cycle.

INTRODUCTION:
The major objective of oral controlled drug delivery system is to deliver drugs for longer period of time to achieve better bioavailability, which should be predictable and reproducible. But this is difficult due to number of physiological problems such as fluctuation in the gastric emptying process, narrow absorption window and stability problem in the intestine. An Ideal drug delivery system should possess two main properties:

1. It should be a single dose for the whole duration of the treatment.

2. It should deliver the active drug directly at the site of action.

Gastroretentive drug delivery system (GRDDS) is one of the novel approach in this area. Oral controlled release dosage forms are the most commonly formulated but still offer highest attention in the area of novel drug delivery systems. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could besupplied continuously to its absorption sites in the GIT.

Poor absorption of many drugs in the lower GIT necessitates controlled release dosage forms to be maintained in the upper GI tract, particularly the stomach and upper small intestine. These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery.

Figure 1: (a) Conventional Dosage Form and (b) Gastric Retentive Drug Delivery System (ref. https://data.epo.org/)

GRDDS are thus beneficial for such drugs by improving their bioavailability, therapeutics efficacity and effective reduction of the dose and improves the drug solubility that is less soluble in a high pH environment. Apart of these advantages, these systems offer various pharmacokinetics advantages like maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels. Gastric retention will provide
advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also prolonged gastric retention time in the stomach could be advantageous for local action in the upper part of the small intestine.

**PHYSIOLOGY OF STOMACH:**

The stomach is an organ with a capacity for storage and mixing. Anatomically the stomach is divided into three regions: Fundus, Body and antrum (pylorus). The proximal part made up of fundus and body which acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.\(^5\) Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH 1–3) 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, interdigestive 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 GIT. The interdigestive motility pattern is commonly called the ‘migrating motor complex’ (‘MMC’) and is organised in cycles of activity and quiescence.\(^9\)

**NEEDS FOR GASTRO RETENTION**\(^11\)

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or are degraded by the alkaline pH they encounter at the lower part of GIT.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
- Particularly useful for the treatment of peptic ulcers caused by H. Pylori Infections.

**IDEAL DRUG CHARACTERISTICS FOR GRDDS**\(^6\)

1. Drugs acting locally in the stomach, e.g. Antacids and drugs for H. Pylori viz., Misoprostol
2. Drugs that are primarily absorbed in the stomach and upper part of GI, e.g. Amoxicillin, Calcium Supplements, Chlordiazepoxide and Cinnarazine
3. Drugs that is poorly soluble at alkaline pH, e.g. Furosemide, Diazepam, Verapamil HCL, Chlordiazepoxide etc.
4. Drugs with a narrow window of absorption in GIT, e.g. Riboflavin, ParaAminobenzoic Acid, Cyclosporine, Methotrexate, Levodopa etc.
5. Drugs which are absorbed rapidly from the GI tract, e.g. Metronidazole, tetracycline.
6. Drugs that degrade or unstable in the colon, e.g. Captopril, Ranitidine HCL, Metronidazol, Metformin HCL.
7. Drugs that disturb normal colonic microbes, e.g. Amoxicillin Trihydrate, antibiotics against Helicobacter pylori.

**UNSUITABLE DRUGS FOR GRDDS**\(^12\)

1. Drugs that have very limited acid solubility. e.g. phenytoin etc.
2. Drugs that suffer instability in the gastric environment. e.g. erythromycin etc.
3. Drugs intended for selective release in the colon. e.g. 5-amino salicylic acid and corticosteroids etc.

**FACTORS CONTROLLING GRDDS**

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm.\(^13\) The most important parameters controlling the GRT of oral dosage forms include : density, size, shape of the dosage form, food intake and its nature, caloric content, frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity, diseased states of the individual (e.g. chronic disease, diabetes etc.) and administration of drugs with impact on GI transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide, cisapride).\(^14\) The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters.\(^15\)

**A. Dosage form related factors**

**Density of dosage forms:** Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach.\(^16\) Both positions may isolate the dosage system from the pylorus. A density of < 1.0 g/ml is required to exhibit floating property.\(^17\) However; the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium.\(^18\)

**Size of the dosage form:** The mean GRT of nonfloating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units.\(^19\) In most cases, the larger the dosage form the greater will be the GRT due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine.\(^20\) Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm.\(^17\) Thus the size of the dosage form appears to be an important factor affecting gastric retention.\(^21\)
Shape of the dosage form: Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.  

Single or multiple unit formulation: Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow coadministration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.  

B. Food intake and its nature

The presence or absence of food in the GIT influences the GRT of the dosage form. Usually the presence of food in the GIT improves the GRT of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows how much gastric emptying time and improve the gastric retention of dosage forms. Food habits affect the GRT in the following ways.  

Fed or unfed state: Under fasting conditions, the GIT motility is characterized by hyperperiods of the migrating myoelectric complex (MMC) that occur every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. It was concluded that as the meals were given at the time when the previous digestive phase had not completed, the floating form could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach.

Nature of meal: Feeding is indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

Caloric content: GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

Frequency of feed: The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

C. Patient related factors

Gender: Generally females showed a comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men.

Age: In case of elder persons, gastric emptying is slowed down, especially those over 70, have a significantly longer GRT.

Posture: GRT can vary between supine and upright ambulatory states of the patient; the floating and non-floating systems behaved differently. In the supine position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions and the floating units remained away from the pylorus. However, in the supine position, the floating units are emptied faster than non-floating units of similar size.

Concomitant drug administration: Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

D. Disease states:

Gastric ulcer, diabetes, hypothyroidism increase GRT. Hyperthyroidism, duodenal ulcers decrease GRT.

E. Volume of GI fluid:

The resting volume of the stomach is 25 to 50 mL. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids.

F. Effect of buoyancy:

On comparison of floating and non-floating units, it was concluded that regardless of their sizes the floating units remained buoyant on the gastric contents throughout their residence in the GIT, while the non-floating units sank and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while they on floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.

Types of dosage form for GRDDS:

A) Floating drug delivery systems (FDDS) and its mechanism:

FDDS is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This system is desirable for drugs with an absorption window in the stomach or in the upper small intestine. This has a less density than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly at a desired rate from the system. After release of the drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuation in plasma drug concentration.

The major requirements for FDDS are:

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 g/mL cm³).
- It must form a cohesive gel barrier.
The inherent low density can be provided by the entrapment of air (e.g., hollow chambers)\textsuperscript{29} or by the incorporation of low density materials (e.g., fatty materials or oils, or foam powder)\textsuperscript{30-32}. These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler\textsuperscript{33}. The good floating behaviour of systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the GIT which may produce irritation. On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce inter and intra-subject availabilities in drug absorption as well as to lower the possibility of dose dumping. Various multiple-unit floating systems like air compartment multiple-unit system, hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method\textsuperscript{34}, microparticles based on low density foam powder\textsuperscript{31}, beads prepared by emulsion gelatin method\textsuperscript{35} etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer-lasting and more reliable release of drugs. Based on the mechanism of buoyancy FDDS can be divided as below:

I. Effervescent Systems

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach, CO\textsubscript{2} is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate\textsuperscript{17}, multiple unit floating pills that generate CO\textsubscript{2} when ingested, floating miniature with core of sodium bicarbonate, lactose and poly vinyl pyrolidone coated with hydroxyl propyl methyl cellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

a. Volatile liquid containing systems

This type of system consists of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains the drug and the second chamber contains the volatile liquid. The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Polyvinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach\textsuperscript{36}. The device inflates, and the drug is continuously released from the reservoir into the gastric fluid.

b. Gas – generating systems

These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO\textsubscript{2}, which gets entrapped in the gellified hydrocolloid layer of the systems, thus decreasing its specific gravity and making it float over chyme\textsuperscript{36,37}. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.
A new multiple type of floating dosage system composed 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 two sublayers to avoid direct contact between the two 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. CO$_2$ was generated by the neutralization reaction between the two effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml. It was found that the system had good floating ability independent of pH and viscosity and the drug (Para‐amino benzoic acid) released in a sustained manner as shown in Fig.5.

II. Non-Effervescent FDDS

Non-effervescent FDDS are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polycrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems includeHPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, polycarbophil, polyacrylate, polystyrene, agar, carrageenans, or algicnic acid are used.

Figure 6: Working principle of hydrodynamically balanced system (ref. www.sciencedirect.com)

The polymer is mixed with drugs and usually administered in HB-capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form. Incorporation of fatty excipients gives low-density formulations reducing their erosion. Madopar LP®, based on the system was marketed during the 1980’s. Effective drug delivery depends on the balance of drug loading and the effect of polymer on its release profile. Several strategies have been tried and investigated to improve efficiencies of the floating hydro dynamically balanced systems.

b. Microporous compartment system

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enter through the aperture dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

c. Alginate beads

Multi-unit floating dosage forms have been developed from freezedried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride.
calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40°C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

**Figure 7:** Formulation of floating hollow microsphere or microballoon (ref. www.pharmainfo.net)

Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosageform are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. These microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

**B. BIO/MUCO-ADHESIVE SYSTEMS:**

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial cell surface or mucin in the stomach. It increases the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The adherence to the gastric wall increases residence time at a particular site, thereby improving bioavailability. Gastric mucosa does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucus by the gastric mucosa to replace the mucus that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used are polycarbophil, carboxylate, lectins, chitosan and angliadin, etc. BDDS are used as a delivery device within the human to enhance drug absorption in a site-specific manner.

**Figure 8:** Bio-adhesion System (ref. www.science direct.com)

The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanisms. These mechanisms are:

1. **The wetting theory,** which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
2. **The diffusion theory** which proposes physical entanglement of mucin strands with the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
3. **The absorption theory,** suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
4. **The electron theory,** which proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material.

**Binding of polymers to the mucin/epithelial surface can be divided into three categories:**

a. **Hydration-mediated adhesion:** Certain hydrophilic polymers have the tendency to imbibe a large amount of water and become sticky, thereby acquiring bioadhesive properties. The prolonged gastroretention of the bio/muco-adhesive delivery system is further controlled by the dissolution rate of the polymer.

b. **Bonding-mediated adhesion:** The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms including physical, mechanical and chemical bonding. Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucus. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e. 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.

c. **Receptor-mediated adhesion:** Certain polymers have the ability to bind to specific receptors on the cell surface. The receptor mediated events serve as a potential approach in bio/muco-adhesion, hence enhancing the gastric retention of dosage forms. Certain plant lectins, like...
tomato lectins, interact specifically with the sugar groups present in mucus or on the glycosal line.

C. EXPANDABLE, UNFOLDABLE AND SWELLABLE SYSTEMS

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction neither singly nor by accumulation. Thus, their configurations are required to develop an expandable system to prolong GRT:

1) A small configuration for oral intake,
2) An expanded gastroretentive form, and
3) A final small form enabling evacuation following drug release from the device.

Thus, gastro-retention is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristaltic and mechanical contractility of the stomach.

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D. HIGH DENSITY SYSTEMS

Gastric contents have a density close to water (1.004 g/cm³). When high density pellets is given to the patient, it will sink to the bottom of the stomach and are entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm³) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm³. The only major drawbacks with this system 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/cm³.

E. MAGNETIC SYSTEMS

This approach to enhance the GRT is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance. The technological approach in rabbits with bioadhesive granules containing ultra-fine ferrite. They guided them to oesophagus with an external magnet for the initial 2 minutes and almost all the granules were retained in the region after 2 hours.

F. RAFT FORMING SYSTEM

Raft System incorporate alginate gels have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating. Raft forming systems have received much attention for the drug delivery for GI infections and disorders. The mechanism includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO₂. Usually, the system ingredients includes an agent forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO₂ to make the system less dense and float on the gastric fluids.

Figure 9: Unfoldable and swellable systems (ref. www.sciencedirect.com)

Unfoldable and swellable systems have been investigated and recently tried to develop an effective GRDDS. Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring, or planner membrane (4 - label disc or 4 - limbed cross) of bioerodible polymer compressed within capsule which extends in the stomach. Swellable systems are also retained in the GIT due to their mechanical properties. The swelling is usually results from osmotic absorption of water. Expandable systems have some drawbacks like problematical storage of macheasilly hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy.

Figure 3: Schematic illustration of the barrier formed by a raft-forming system. (ref. http://www.pharmainfo.net/reviews/gastroretentive-drug-delivery-system-overview)
An antacid raft forming floating system contains a gel forming agent (e.g., sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodiumalginate gel (raft), which when comes in contact with gastric fluids, the raft floats on the gastric fluids and prevents the reflux of the gastric contents (i.e., gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus.  

G. SUPER POROUS HYDROGEL SYSTEMS  
These swellable systems differ sufficiently from the conventional types to warrant separate classification. Super porous hydrogel that expand dramatically (hundreds of times their dehydrated form within a matter of seconds) when immersed in water. With pore size ranging, 10 nm to 10 µm, absorption window by conventional hydrogel is a very slow process and several hours may be needed to reach an equilibrium state during which parameter evacuation of the dosage form may occur. In this approach to improve GRT super porous hydrogel of average pore size less than 100 µm, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formation of hydrophilic particulate material.  

H. SWELLING SYSTEMS  
These are the dosage forms, which after swallowing; swell at an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as “plug type systems”, since they exhibit the tendency to remain lodged at the pyloric sphincter. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selection of proper molecular weight polymer, and swelling of the polymer retards the drug release. On coming in contact with gastric fluid, the polymer imbibles water and swells. The extensive of these polymers is due to the presence of physical/chemical cross-links in the hydrophilic polymer network.  

Figure 1: Swellable tablet in stomach (ref: www.pharmainfo.net)  

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS  
1) The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this GRDDS in comparison to the administration of non-GRDDS. There are several different factors related to absorption and transit of the drug in the GIT that act concomitantly to influence the magnitude of drug absorption.  
2) In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.  
3) For drugs with relatively short half life, sustained release may result in a flip-flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.  
4) They also have an advantage over their conventional systems as it can be used to overcome the adversities of the GRT as well as the GET. As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because of low density.  
5) GRDDS can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.  
6) The controlled, slow delivery of drug form GRDF provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.  
7) Continuous input of the drug following CR-GRDF administration produces blood drug concentrations within a narrower range compared to the IR dosage forms. Thus, GRDF minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.  
8) Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented.  
9) In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Thus slow input of the drug into the body was shown that gastroretentive drug delivery system can minimize the counter activity of the body leading to higher drug efficiency.  
10) Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.  
11) The sustained mode of drug release from gastroretentive dosage form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.  

LIMITATIONS OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS  
GRDDS have potential in improving BA of drugs exhibiting ‘absorption window’. However they have certain limitations. One of the major disadvantages of the
floating system is therefore required to maintain high levels of fluids in the stomach for the delivery system to float and work efficiently.  

1) Require a higher level of fluids in the stomach.  
2) Not suitable for drugs that may cause gastric lesions e.g. Non-steroidal anti-inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the GIT.  
3) Drugs intended for selective release in the colon e.g. 5-amino salicylic acid and corticosteroids etc.  
4) The floating systems in patients with achlorhydria can be questionable in case of swellable system.  
5) Retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.  
6) The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.  
7) Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique. Similarly retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.  
8) In all the above systems the physical integrity of the system is very important and primary requirement.  
9) The residence time in the stomach depends upon the digestive state. Hence FFDS should be administered after the meal.  
10) The ability to float relies on the hydration state of the dosage form. In order to keep these tablets floating in vivo, intermittent administration of water (a tumbler full, every 2 hours) is beneficial.  
11) The ability of the drug to remain in the stomach depends upon the subject being positioned upright.  
12) Nifedipin like drug can’t be candidate for FDDS since the slow gastric emptying may lead to the reduced systemic bio-availability.  

REFERENCES:  

Table 1: Some marketed preparations of GRDDS available in the Market

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam Floating capsule</td>
<td>Valrelease®</td>
</tr>
<tr>
<td>Benserazide and L-Dopa</td>
<td>Madopar®</td>
</tr>
<tr>
<td>Aluminium – Magnesium antacid</td>
<td>Topalkan®</td>
</tr>
<tr>
<td>Antacid preparation</td>
<td>AlmagateFlot-Coat®</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Cifran OD</td>
</tr>
<tr>
<td>Metformin HCL</td>
<td>Glumetza GRTM</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Cyotec</td>
</tr>
<tr>
<td>Aluminium Hydroxide</td>
<td>Liquid Gavison</td>
</tr>
<tr>
<td>Ferrous sulphate</td>
<td>Convirone</td>
</tr>
</tbody>
</table>

CONCLUSIONS:  
Controlled release gastroretentive dosage forms (CR-GRDDS) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. Based on the literature surveyed, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half-life.  

FUTURE POTENTIAL FOR GRDDS:  
While the control of drug release profiles has been a major aim of pharmaceutical research and development in the past two decades, the control of GI transit profiles could be the focus of the next two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. Soon, the so-called ‘once-a-day’ formulations may be replaced by novel gastroretentive products with release and absorption phases of approximately 24 hours.
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