Gastroretentive drug delivery system – an overview

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Abstract
Gastro-retentive drug delivery system (GRDDS) is one of the novel approaches in the field of oral sustained release drug delivery. It is a widely employed approach to retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability. Different innovative approaches like high density (sinking), floating, bio- or mucoadhesive, expandable, unfoldable, super porous hydrogel and magnetic systems, magnetic field assisted gastro-retention, plug type swelling system, muco-adhesion technique, floating system with or without effervescence are being applied to fabricate GRDDS. The present review mainly focuses on features and various physiological considerations for development of GRDDS.

Key words: Gastro retentive drug delivery system, Non floating and Floating system

INTRODUCTION
Despite the tremendous advancement in drug delivery, oral route is the most preferred route to the systemic circulation due to the ease of administration, low cost of drug, patient compliance and flexibility in formulation. About 90% of all drugs used to produce systemic effects are administered by oral route. Of the drugs that are administered orally, solid oral dosage forms represent the preferred class of products [1]. However, many drugs are absorbed from specific sites and they require release at that site only for better absorption. Drug absorption in the gastrointestinal tract is a highly variable procedure and it depends upon the factors such as a gastric emptying process, gastrointestinal transit time of dosage forms, drug release from the dosage form, and site of absorption of drugs [2,3]. Drugs that are easily absorbed from the gastro intestinal 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. Also, the drugs which have a narrow absorption window (NAW) in the upper part of the GIT are not suitable for oral sustained release drug delivery system gastric emptying time as tablets have 2.7 ± 1.5 hours (h) stomach transit and 3.1 ± 0.4 h intestinal transit time [4], thus the bioavailability of such drugs having an absorption window in the stomach is generally limited. Gastro retentive drug delivery is one of those approaches to prolong the gastric residence time, thereby targeting a site specific drug release in the stomach of local or systemic effects. These dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time of the drugs. It will release the drug in the stomach in a controlled manner, so that the drug could be supplied continuously to the absorption site in GIT [5].

GRDDS are beneficial for such drugs by improving them

- Bioavailability
- Therapeutics efficiency and
- Possible reduction of the dose.
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels
- Reduce drug wastage
- Improves solubility of drugs that are less soluble at high pH environment (e.g. Weakly basic drug like Domperidone, papaverine)

Factors affecting gastric retention time of the dosage form

- **Density** - the density of the dosage form should be less than that of the gastric contents (1.004g/ml)

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- **Size** - Dosage form having diameter of more than 7.5mm have more gastric residence time than that of 9.9mm diameter dosage form [6].
- **Shape of the dosage form** - A diameter resided in the stomach for a longer period than other devices of similar size. The single or multiple unit formulation -multiple unit formulation show a greater predictable release profile and insignificant impairing of the performance due to failure of the units, allow co administration of units with different release profile or containing incompatible substances and permit larger margin of safety against dosage form failure compared with single unit dosage form.
- **Fed or unfed state** - under fasting conditions, the gi motility is characterized by periods of strong motar activity that occurs every 1.5-2hrs. The MMC sweeps undigested material from the stomach and if the timing of the formulation coincides with that of MMC, the GRT of the unit can be very short, however in fast state MMC is delayed and GRT is longer[7].
- **Nature of meal** - feeding of undigestible polymers or fatty acids can change the motility pattern of the stomach to a fed state, thus decreasing gastric emptying rate and prolonging drug release.
- **Caloric content** - GRT can be increased by 4-10 with a meal that is high in protein and fat.
- **Frequency the meal** - feeding increase over 400 min when successive meals given are compared with the single meal due to low frequency of MMC [8,9].
- **Gender** - mean ambulatory GRT in male (3.4hrs) is less compared with the age and race matched female counterparts (4.6hrs) regardless of height, weight and body surface [10].
- **Age** - people with age more than 70 have a significant longer GRT.
- **Concomitant drug administration** - tocolinergic like atropine and propetheline, opiates like codeine can prolong GRT [11].

**Drug candidate suitable for Gastroretentive drug delivery system**

- Drugs those are locally active in the stomach e.g. misroprostol, antacids etc.
- Drug which are absorbed rapidly from Gl.eg:L-DOPA,paro amino benzoicacid, furosemide, riboflavin
- Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
- Drugs that disturb normal colonic microbes like antibiotics against Helicobacter pylori
- Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl [12].

**What is the need of GRDDS?**

There occurs a quick elimination of certain drugs, that have been absorbed from the gastrointestinal tract (usually having short half-lives), from circulatory system due to which frequent dosing is required. To sort out this matter, innovative method gastro retentive drug delivery systems are incorporate.

They have efficient plasma drug concentration thereby reduce dosing frequency. Another Method is to incorporate this systemic concentration, there by effectively reduces variations in plasma drug concentration by delivering the drug in a controlled and reproducible fashion.

**Drugs Those are Unsuitable for Gastroretentive Drug Delivery Systems**

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. eg: Corticosteroids

**Types of Gastroretentive Dosage Form**

Gastroretentive drug delivery system can be divided into

**Non Floating System**

- a. High Density (Sinking) Drug Delivery System:
- b. Bioadhesive or mucoadhesive system
- c. Magnetic system
d. Expandable system

**Floating Drug Delivery System**

- a. Effervescent System
  - i. Gas generating
  - ii. Volatile liquid containing system
    - a. Intra gastric floating gastrointestinal drug delivery system
b. Intra-gastric osmotically controlled drug delivery system
c. Inflatable gastrointestinal drug delivery system

b. Non effervescent system:
   i. Hydrodynamically balanced system
   ii. Microballoons or hollow microspheres
   iv. Microporous compartment
   iii. Alginate beads

Fig 1. Rationale for The Use of GRDDS

Fig 2. Schematic presentation of various approaches for gastroretention

Fig 3. High density system
**Non Floating System**

**a. High Density (Sinking) Drug Delivery System**

In this approach formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulfate, zinc oxide and titanium oxide so that the density of the formulation exceeds the density of the normal gastric content (figure 3). These materials increase the density up to 1.5-2.4 gm/cm³. Depending on density, the GI transit time of pellets can be extended from an average of 5.8 to 25 hours. But the effectiveness of this system in human beings...
was not observed [13] and no formulation has been marketed.

b. **Bioadhesive or mucoadhesive system**

The gastric retention time is extended by adhering the bioadhesive system for gastric mucous membrane (Fige 4). The adherence of the delivery system to the gastric wall increases residence time thereby improving bioavailability. The chemicals used for the mucoadhesion purpose include polycarbophil, carbopol, lectin, chitosan, carboxy methylcellulose, gliadin etc [14]. Novel adhesive material derived from fimbrae of bacteria or its synthetic analogues have also been tried for the attachment to the gut. However, the gastric mucoadhesive force does not tend to be strong enough to resist the propulsion force of the stomach wall. The continuous production of mucus and dilution of the gastric content is another limitation for such type of system. Many investigators have tried out a synergestic approach between floating and bioadhesion system.

c. **Magnetic system**

In this system, the dosage form contains a small magnet and another magnet is placed on the abdomen over the position of the stomach. The external magnet should be placed with a degree of precision which may decrease the patient compliance.

d. **Expandable System**

These systems are capable of expanding and retain in the stomach for longer periods. These are usually formulated as a capsule containing dosage form folded and compact form. After being exposed to stomach environment, capsule shell disintegrates and dosage form expands preventing its exit through the stomach. By using a suitable polymer, sustained and controlled drug delivery can be achieved.

**Floating Drug Delivery System**

a. **Effervescent System:** These systems are further classified as below

1. Gas generating system:
   The main mechanism is involved in this system is the production of CO2 gas due to reaction between sodium bi carbonate, citric acid and tartaric acid. The gas produced results in the reduction of density of the system, thereby making it float on the gastric fluids. Salts and citric/tartaric acid release CO2, which entrapped in the jellified hydrocolloid layer of the system which decrease its specific gravity and making it float over chime [15]. The system consist of a sustain release pill as seed surrounded by double layers. The inner layer is an effervescent layer containing sodium bi carbonate and tartaric acid. The outer layer is of a swellable membrane layer containing PVA shellac.

2. **Volatile liquid containing system**

These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasify at body temperature to cause the inflation of the chamber in the stomach. These systems osmotically control floating system containing a hollow definable unit. These are two chambers in the system first contain the drug and the second chamber containing the volatile system. These are classified as

a. **Intra gastric floating gastrointestinal drug delivery system**

This system (Fig 5) contains a floatation chamber which contains vacuum or an inert, harmless gas and a micro porous compartment enclosing drug reservoir.

b. **Inflatable gastrointestinal drug delivery system**

These systems possess inflatable chamber containing liquid ether (figure 6) which gasifies at body temperature to inflate the stomach. Inflatable chamber contains bio erodible polymer filament (e.g. Copolymer of poly vinyl alcohol and poly ethylene) that gradually dissolves in gastric fluid and finally cause an inflatable chamber to release gas and collapse.

c. **Intra-gastric osmotically controlled drug delivery system**

It is composed of osmotic pressure controlled drug delivery device and an inflatable floating capsule. In the stomach, inflatable capsule disintegrates and release the osmotically controlled drug delivery system which contains two components: drug reservoir compartment and osmotically active compartment.
Superporous hydrogels are an excellent example, working on this approach. The dosage form swells significantly to several times of original volume upon contact with gastric fluid, the gastric contraction pushes the dosage form to the pylorus but due to the larger size of the dosage form, the contractions slips over the surface of the system, due to which the dosage form pushes back into the stomach.

Non-effervescent system can be further divided into: hydrodynamically balanced system, Microballoons, alginate beads, and microporous compartment.

i. Hydrodynamically balanced system
It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug Delivery Systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations.

ii. Microballoons: Microballoons (Hollow microsphere) are in the strict sense, empty particles of spherical shape without core. These microspheres are characteristically free flowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 micrometers. Microballoons loaded with drug in their outer polymer shell are prepared by a novel methods such as solvent evaporation or solvent diffusion/evaporation to create a hollow inner core. The drug and an enteric acrylic polymer mixture are dissolved in ethanol/dichloromethane solution and it is poured into an agitated solution of Poly Vinyl Alcohol (PVA) that as thermally controlled at 40 °C.
After the formation of stable emulsion, the organic solvent is evaporated from the emulsion by increasing the temperature under pressure or by continuous stirring. The gas phase is generated in the droplet of dispersed polymer by the evaporation of dichloromethane and thus formed the hollow internal cavity in the microsphere of the polymer with drugs.

**Fig 8. Hydrodynamically balanced system**

iii. Microporous compartment: In this system, drug reservoir is encapsulated inside a microporous compartment having pores along its top and bottom walls. The floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug in the stomach and proximal part of the small intestine for absorption.

iv. Alginate beads: Freeze dried calcium alginites have been used to develop multi unit floating dosage forms [17]. By dropping sodium alginate solution into aqueous solution of calcium chloride spherical beads of about 2.5 mm diameter can be prepared. These beads are separated and air dried. This results in the formation of aporous system which remains buoyant in the stomach.

**Evaluation Parameters of GRDDS**

Evaluation parameters of GRDDS generally include:

**Drug-excipient interaction**

It is done by using FTIR and HPLC. The appearance of a new peak and/or disappearance of original drug or excipient peaks indicate the drug excipients interaction.

**Floating lag time**

It is the time taken to emerge tablet onto the surface after it is kept in to the dissolution medium. It is measured in minutes or seconds.

**In vitro drug release and duration of floating**

It is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37±2°C in simulated gastric fluid of pH 1.2. Aliquots of the samples are collected and analyzed for the drug content. The time for which the drug remains floating on the surface of the medium is the duration of the floating time.

**In vivo evaluation of gastric retention**

Analysis of the position of the dosage form in the GIT involves an imaging technique such as γ-scintigraphy and X-ray.
In γ-scintigraphy, a small amount of stable isotope is compounded in the dosage forms during its preparation. The inclusion of a γ-emitting radio-nuclide in a formulation allows indirect external observation using a γ-camera or scinti scanner. For x-ray, barium sulfate is used as a contrast medium. It helps to locate a dosage form in the GIT by which one can predict and correlate the gastric emptying time and the passage of the dosage form. In addition, gastroscopy and ultrasonography studies can be included in the in vivo evaluation of GRDDS. Gastroscopy comprises of per-oral endoscopy, used with a fiberoptic and video system. Ultrasonography is not routinely used in the evaluation of GRDDS. In vivo plasma profile can also be obtained by performing the study in a suitable animal model.

**Water uptake study**

It is done by immersing the dosage form in simulated gastric fluid at 37°C and determining the dimensional changes, such as diameter and thickness, at regular interval of time. After the stipulated time the swollen tablets are weighed and water uptake is measured in the terms of percentage weight gain, as given:

$$WU = \frac{(W_t - W_0) \times 100}{W_0};$$

In which, $W_t$ and $W_0$ are the weight of the tablet after time $t$ and initially, respectively. The tablets are also evaluated for hardness, friability, weight variation etc. which are applicable for conventional instant release tablets. For the multiple unit dosage forms like microsphere following tests are also essential apart from the above tests.  
- Morphological and dimensional analysis: It is done with the aid of scanning electron microscopy and optical microscope  
- Percentage yield of microsphere.  
- Entrapment efficiency: The drug is extracted by suitable method and analyzed to find out the amount of drug present. [18,19]

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**Table 1. Commercially Available Marketed Products**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug</th>
<th>Dosage forms</th>
<th>Dose</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cifran O.D</td>
<td>Ciprofloxacin</td>
<td>Tablet</td>
<td>500mg, 1 gm</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Liquid Gavison</td>
<td>Al hydroxide and Mg carbonate</td>
<td>Liquid</td>
<td>95mg and 358 mg respectively</td>
<td>Glaxo Smith Kline, India</td>
</tr>
<tr>
<td>Madopar</td>
<td>Levodopa and Benserazide</td>
<td>Capsule</td>
<td>100mg and 25mg respectively</td>
<td>Roche Products, USA</td>
</tr>
<tr>
<td>Glumetza</td>
<td>Metformin Hydrochloride</td>
<td>Tablet</td>
<td>500mg and 1000mg</td>
<td>Depomd, Canada</td>
</tr>
<tr>
<td>Valrelease</td>
<td>Diazepam</td>
<td>Capsule</td>
<td>15 mg</td>
<td>Hoffmann-LaRoche, USA</td>
</tr>
<tr>
<td>Topalkan</td>
<td>Aluminium – Magnesium antacid</td>
<td>Liquid alginate</td>
<td>---------------</td>
<td>Pierre Fabre Drug, France</td>
</tr>
<tr>
<td>Cyotec</td>
<td>Misoprostol</td>
<td>Bilayer capsule</td>
<td>100 mcg/200 mcg</td>
<td>Pharmacia, USA</td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Colloidal gel</td>
<td>---------------</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Oflin OD</td>
<td>Ofloxacin</td>
<td>Tablet</td>
<td>400mg</td>
<td>Ranbaxy, India</td>
</tr>
</tbody>
</table>

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**CONCLUSION**

Gastroretentive drug delivery systems have emerged as current approaches of enhancing bioavailability and controlled delivery of drugs that exhibit an absorption window. Gastroretentive drug delivery approaches comprised mainly of floating, bioadhesive, swelling, magnets, and high density. These systems not only provide controlled release of the drug, but also present the drug in an absorbable form at the regions of optimal absorption. All these drug delivery systems have their own advantages and drawbacks. To design a successful GRDDS, it is necessary to take into consideration the physicochemical properties of the drug, physiological events in the GIT, formulate strategies, and correct combination of drug and excipients.

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**CONFLICT OF INTEREST**

No conflict of interest.
REFERENCES


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