

# **GASTRORETENTIVE DRUG DELIVERY SYSTEM-AN OVERVIEW**

**R.Margret Chandira\***, Debjit Bhowmik ,Chiranjib, B.Jayakar  
Vinayaka missions college of pharmacy  
Vinayaka missions university  
Salem-636008, Tamilnadu

**E-mail:bhowmikdebjit@yahoo.co.in**

## **ABSTRACT**

In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. Gastroretentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Different approaches for gastroretentive dosage forms include floating, raft, expanding or swelling, bioadhesive or mucoadhesive and high/low-density systems. The oral controlled drug delivery systems (DDS) should be primarily aimed to achieving more predictable and increased bioavailability of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, useful for drugs acting locally in the GIT, drugs which are poorly soluble and unstable in intestinal fluids. These systems are advantageous in improving GIT absorption of drug with CR due to specific site absorption limitations. Among the various gastro retentive systems, gastric floating drug delivery systems (GFDDS) offer numerous advantages over the gastric retentive systems. These systems have a density lower than the gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach <sup>2</sup>.

## **INTRODUCTION**

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed <sup>1</sup>. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine).

*Floating Drug Delivery Systems* (FDDS) 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.

The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules. In response, a large number of chemical entities have been introduced, of which some have absorption all over the gastrointestinal tract (GIT), some have absorption windows (i.e. absorption sites, especially the upper part of the small intestine) and some drugs have poor solubility in intestinal media. The drugs belonging to the second and third categories, and the drugs which are required for local action in the stomach, require a specialized delivery system. All the

above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by floating drug delivery systems (FDDS).

To date, a number of FDDS involving various technologies, carrying their own advantages and limitations were developed such as, single and multiple unit hydro dynamically balanced systems (HBS), single and multiple unit gas generating systems, hollow microspheres and raft forming systems<sup>2</sup>.

The hydrodynamic balanced system (HBS) also called Floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions<sup>3</sup>. The retentive characteristics of the dosage form are not significant for the drugs that:

- 1) Are insoluble in intestinal fluids
- 2) Act locally
- 3) Exhibit site-specific absorption.

However, the system can be used for most of the drugs where controlled (sustained) release of the dosage form is desired by the oral route.

The formulation of the dosage form must comply with three major criteria for HBS.

- 1) It must have sufficient structure to form a cohesive gel barrier.
- 2) It must maintain an overall specific gravity less than that of gastric content.
- 3) It should dissolve slowly enough to serve as a “Reservoir” for the delivery system.

Floating systems are one of the important categories of drug delivery systems with gastric retentive behavior. Drugs that could take advantage of gastric retention include:

furosemide, cyclosporine, allopurinol ciprofloxacin and metformin. Drugs whose solubility is less in the higher pH of the small intestine than the stomach (e.g. chlordiazepoxide and cinnarizine, the drugs prone for degradation in the intestinal pH (e.g. captopril), and the drugs for local action in the stomach (e.g. misoprostol) can be delivered in the form of dosage forms with gastric retention. Antibiotics, catecholamines, sedative, analgesics, anticonvulsants, muscle relaxants, antihypertensive and vitamins can be administered in HBS dosage form.<sup>4, 5,6,7,8</sup>

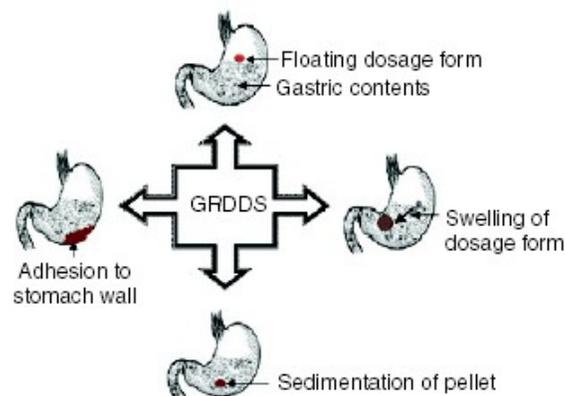
Drugs reported to be used in the formulation of floating dosage forms are:

Chlorpheniraminemaleate, Theophylline, Furosemide, Ciprofolxacin, Pentoxifyfillin, Captopril, Acetylsalicylicacid, Nimodipine, Amoxycillintrihydrate, VerapamilHCl, Isosorbidedinitrate, Sotalol, Atenolol, Isosorbidemononitrate, Acetaminophen, Ampicillin, Cinnarazine, Diltiazem, Florouracil, Piretanide, Prednisolone, Riboflavin- 5'Phosphate.

Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

### **Gastroretentive dosage form (GRDF):**

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDF or GRDS).



***Figure: Classification of gastroretentive drug delivery systems***

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.<sup>14</sup>

Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as<sup>15</sup> –

- 1) This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To overcome this problem, erodible, gastroretentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.
- 2) GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides, tetracyclines etc.), are taken up only from very specific sites of the GI mucosa.
- 3) The retentive characteristics of the dosage form are not significant for the drugs that:
  - 4) Are insoluble in intestinal fluids.
  - 5) Act locally.

- 6) Exhibit site-specific absorption.

However, the system can be used for most for the drugs where controlled (sustained) release of the dosage form is desired by the oral route.

The formulation of the dosage form must comply with three major criteria for HBS.

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### **ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM**

Gastro retentive drug delivery systems have numerous advantages listed below:

- 1) The principle of HBS can be used for any particular medicament or class of medicament.
- 2) The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.
- 3) The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
- 4) The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.
- 5) Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolve drug available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.
- 6) When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such circumstances it may

be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

- 7) Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
- 8) Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.
- 9) Certain types of drugs can benefit from using gastro retentive devices. These include:
  - Drugs acting locally in the stomach;
  - Drugs those are primarily absorbed in the stomach;
  - Drugs those are poorly soluble at an alkaline pH;
  - Drugs with a narrow window of absorption;
  - Drugs absorbed rapidly from the GI tract; and
  - Drugs those degrade in the colon.

### **DISADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS**

- 1) There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
- 2) Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
- 3) Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

## **APPROACHES TO GASTRIC RETENTION** <sup>9, 10, 11,12,13,14</sup>

Several approaches have been attempted in the preparation of gastro-retentive drug delivery systems. These include floating systems, swell able and expandable systems, high density systems, bioadhesive systems, altered shape systems, gel forming solution or suspension systems and sachet systems.

Various approaches have been followed to encourage gastric retention of an oral dosage form. Floating systems have low bulk density so that they can float on the gastric juice in the stomach. The problem arises when the stomach is completely emptied of gastric fluid. In such a situation, there is nothing to float on. Floating systems can be based on the following:

**f Hydrodynamically balanced systems (HBS)** – incorporated buoyant materials enable the device to float;

**t Effervescent systems** – gas-generating materials such as sodium bicarbonates or other carbonate salts are incorporated. These materials react with gastric acid and produce carbon dioxide, which entraps in the colloidal matrix and allows them to float;

**d Low-density systems** -- have a density lower than that of the gastric fluid so they are buoyant;

**b Bioadhesive or mucoadhesive systems** – these systems permit a given drug delivery system (DDS) to be incorporated with bio/mucoadhesive agents, enabling the device to adhere to the stomach (or other GI) walls, thus resisting gastric emptying. However, the mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

**High-density Systems** - 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  $3\text{g/cm}^3$ ) 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 diameter of the pellets, although many conflicting reports stating otherwise also abound in literature.

Commonly used Excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to  $1.5\text{--}2.4\text{ g/cm}^3$ . However, no successful high density system has made it to the market.

**s Large Single- unit Dosage Forms** - these dosage forms are larger than the pyloric opening and so are retained in the stomach. There are some drawbacks associated with this approach. Permanent retention of rigid large-sized single-unit forms can cause bowel obstruction, intestinal adhesion and gastroplasty.

**c Co-administration of gastric- emptying delaying drugs** - this concept of simultaneous administration of a drug to delay gastric emptying together with a therapeutic drug has not received the favour of clinicians and regulatory agencies because of the questionable benefit-to-risk ratio associated with these devices.

The stomach is a size-filtering system and so it would seem ideally suited to retaining a DDS that is larger than the pylorus. The drawback is that the DDS is not small enough to be taken orally if sizes larger than the pylorus are required. Several systems have been investigated to encourage gastric retention using increasing size of DDS. Systems have been based on expansion due to gases and swelling due to intake of external liquids.

**b Raft systems incorporate alginate gels** – these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating of raft on gastric fluid.

## **METHODS FOR PREPARING FLOATING DOSAGE FORM**

Following approaches can be used for preparing floating dosage forms: <sup>21, 22</sup>

- (1) Using gel forming hydrocolloids such as hydrophilic gums, gelatin, alginates, cellulose derivatives, etc.
- (2) Using low density enteric materials such as methacrylic polymer, cellulose acetate phthalate.
- (3) By reducing particle size and filling it in a capsule.
- (4) By forming carbon dioxide gas and subsequent entrapment of it in the gel network.
- (5) By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.
- (6) By incorporation of inflatable chamber which contained in a liquid e.g. solvent that gasifies at body temperature to cause the chambers to inflate in the stomach.

The factors which govern the effectiveness of active medicaments in HBS are:

- 1) Amounts of active medicament to produce therapeutic effect.
- 2) Bulk density
- 3) Hydrophilic and hydrophobic properties
- 4) Stability in gastric fluids.

Fig: 1 is showing the floating drug delivery in stomach and fig: 2 demonstrate the mechanism of floating drug delivery systems.

Fig: → Diagram of Floating Drug Delivery System

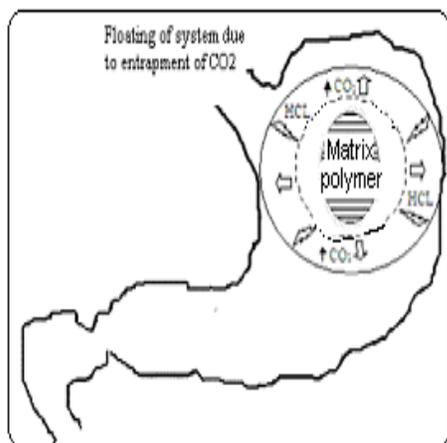
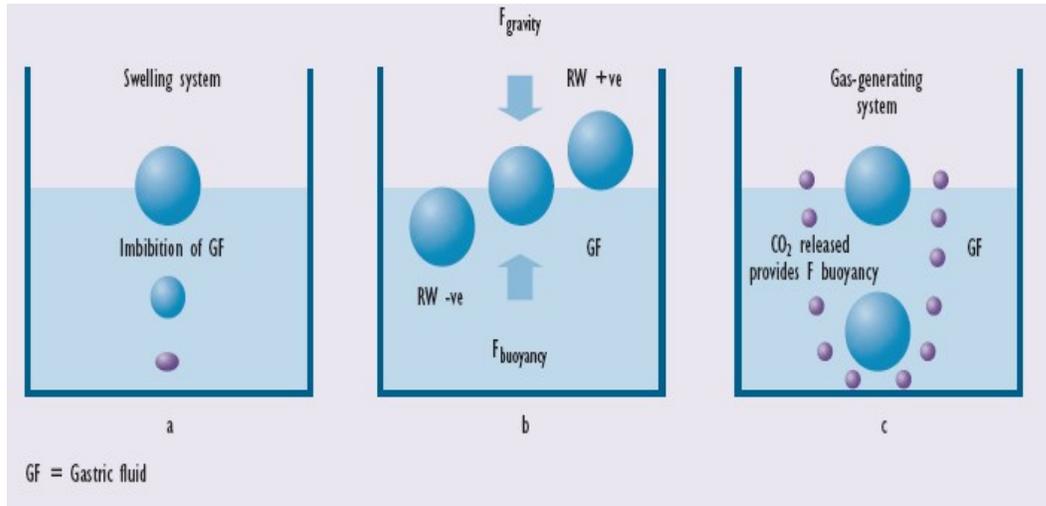


Fig: → Mechanism of Floating Drug Delivery System



## **FACTORS AFFECTING THE GASTRORETENTIVE SYSTEM**

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system:

- Density – gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density;
- Size – dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm;
- Shape of dosage form – tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours 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 co-administration 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;

Fed or unfed state – under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs 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;

- Nature of meal – feeding of 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;
- Gender – mean ambulatory GRT in males ( $3.4 \pm 0.6$  hours) is less compared with their age and race matched female counterparts ( $4.6 \pm 1.2$  hours), regardless of the weight, height and body surface);
- Age – elderly people, especially those over 70, have a significantly longer GRT;
- Posture – GRT can vary between supine and upright ambulatory states of the patient;
- Concomitant drug administration – anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.
- Biological factors – diabetes and Crohn's disease, etc.

## LIMITATIONS <sup>1</sup>

- 1) The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach
- 2) Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
- 3) The dosage form should be administered with a minimum of glass full of water (200-250 ml).
- 4) The drugs, which are absorbed throughout gastro-intestinal tract, which under go first-pass metabolism (nifedipine, propranolol etc.), are not desirable candidate.
- 5) Some drugs present in the floating system causes irritation to gastric mucosa.

## MARKETED PRODUCTS OF GRDDS

- Some of the marketed formulations are listed as follows: <sup>14,16,17,18</sup>

<b>Brand name</b>	<b>Delivery system</b>	<b>Drug (dose)</b>	<b>Company name</b>
Valrelease®	Floating capsule	Diazepam (15mg)	Hoffmann-LaRoche, USA
Madopar® HBS (Prolopa® HBS)	Floating, CR capsule	Benserazide (25mg) and L-Dopa (100mg)	Roche Products, USA
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide (95 mg), Mg Carbonate (358 mg)	GlaxoSmithkline, India
Topalkan®	Floating liquid alginate preparation	Al – Mg antacid	Pierre Fabre Drug, France
Almagate Flot coat®	Floating dosage form	Al – Mg antacid	-----
Conviron®	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Cytotech®	Bilayer floating capsule	Misoprostol (100µg/200µg)	Pharmacia, USA
Cifran OD®	Gas-generating floating form	Ciprofloxacin (1gm)	Ranbaxy, India

**Table No. : List of drugs along with floatable drug delivery systems**

SR. NO.	DOSAGE FORM	DRUGS
1	Microspheres	Aspirin, Grisiofulvin, p-nitroanilline, Ibuprofen, Terfinadine, Tranilast.
2	Granules	Diclofenac sodium, Indomethacin, Predmisolone
3	Films	Cinnarizine
4	Powders	Several basic drugs
5	Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-Dopa, Benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid
6	Tablets/pills	Acetaminophen, Acetylsalicylic acid, Amoxicillin trihydrate, Ampicillin, Atenolol, Chlorpheniramine, Cinnazirine, Diltiazem, Fluorouracil, Isosorbide mononitrate, Isosorbide dinitrate, p-aminobenzoic acid, Piretanide, Prednisolone, Quinidine gluconate, Riboflavin-5'-phosphate, Sotalol, Theophylline, Verapamil HCl

### **CONCLUSION**

A novel floating controlled-release drug delivery system was formulated in an effort to increase the gastric retention time of the dosage form and to control drug release. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastroretentive dosage forms that will provide us with new and important therapeutic options. Floating matrix tablets are designed to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability

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