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## Floating Drug Delivery System-A Review

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### Abstract

Floating Drug delivery system are designed to prolong the gastric residence time after oral administration, at particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. 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. Floating 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. Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. Treatment of gastrointestinal disorders such as gastro-esophageal reflux. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site. Ease of administration and better patient compliance. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.

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### 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). 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. 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. 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. Drugs reported to be used in the formulation of floating dosage forms are: Floating microspheres (aspirin, griseofulvin, p-nitroaniline, ibuprofen, terfenadine and tranilast), floating granules (diclofenac sodium, indomethacin and prednisolone), films (cinnarizine), floating capsules (chlordiazepoxide hydrogen chloride, diazepam, furosemide, misoprostol, L-Dopa, benserazide, ursodeoxycholic acid and pepstatin) and floating tablets and pills (acetaminophen, acetylsalicylic acid, ampicillin, amoxicillin trihydrate, atenolol, diltiazem, fluorouracil, isosorbide mononitrate, para aminobenzoic acid, piritamide, theophylline and verapamil hydrochloride, etc.). Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

#### ***Advantages of floating drug delivery system***

Floating 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 dissolved 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 diarrhoea, 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 floating 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***

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:

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

⇒ ***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;

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

⇒ ***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.

⇒ ***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.

⇒ ***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.

⇒ *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***

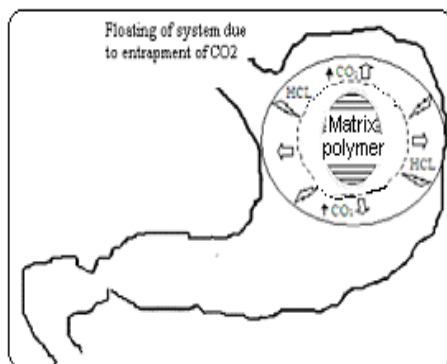
Following approaches can be used for preparing floating dosage forms:

- (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: The floating drug delivery in stomach**



***Factors affecting the floating drug delivery 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**

- 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 undergo first-pass metabolism (nifedipine, propranolol etc.), are not desirable candidates.
- 5) Some drugs present in the floating system cause irritation to gastric mucosa.

### **Marketed products of GRDDS**

Some of the marketed formulations are listed as follows:

<b>Table 1 → Marketed Products of GRDDS</b>			
<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 FDSS	Ferrous sulphate	Ranbaxy, India
Cytotech®	Bilayer floating capsule	Misoprostol (100µg/200µg)	Pharmacia, USA
Cifran OD®	Gas-generating floating form	Ciprofloxacin (1gm)	Ranbaxy, India

### ***Applications and technologies***

- 1) Recent study indicated that the administration of diltiazem floating tablet twice a day might be more effective compared to normal tablets in controlling the blood pressure of hypertensive patient.
- 2) Madopar® HBS- containing L-dopa and benserazide- here drug was released and absorbed over a period of 6-8 hour and maintain substantial plasma concentration for parkinson's patients.
- 3) Cytotech® -- containing misoprostol, a synthetic prostaglandin- E1 analog, for prevention of gastric ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDS).
- 4) As it provides high concentration of drug within gastric mucosa, it is used to eradicate pylori (A causative organism for chronic gastritis and peptic ulcers).
- 5) 5-Fluorouracil has been successfully evaluated in patients with stomach neoplasm.
- 6) Developing HBS dosage form for tacrine provides a better delivery system and reduces its GI side effects in alzheimer's patients.
- 7) Treatment of gastric and duodenal cancers.
- 8) Alza corporation has developed a gastroretentive platform for the OROS® system, which showed prolong residence time in a dog model as the product remain in the canine stomach at 12 hrs. post dose and was frequently present at 24 hrs.

### ***Gastro retentive 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).

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 override this problem, erodible, gastroretentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.
- 2) GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating *Helicobacter pylori* from the submucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric

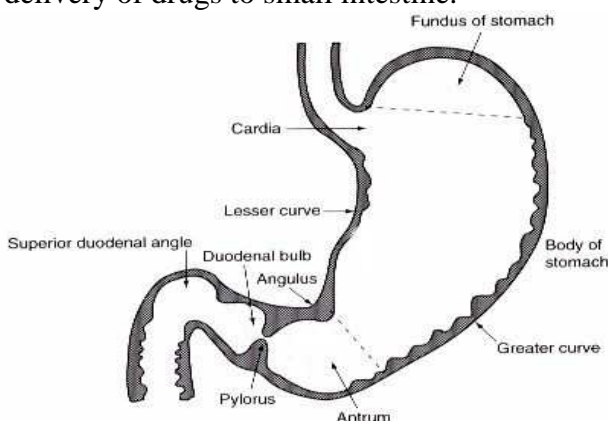
carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).

- 3) 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.

### **Biological aspects of GRDFs:**

#### **Role of GI tract: Stomach**

The stomach is J-shaped organ located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach. It provides barrier to the delivery of drugs to small intestine.



**Fig. 2 : Anatomy of Stomach**

The stomach is divided into three anatomical regions. i) Fundus ii) Body and iii) Pylorus (or antrum). The proximal stomach consisted of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying. Gastric emptying occurs both in fasting as well as fed states.

The GI tract is always in a state of continuous motility. There are two modes of motility pattern. The digestive mode and interdigestive mode. In case of fasted state an interdigestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr. This electrical activity is termed as interdigestive myoelectric cycle or migrating myoelectric complex (MMC), which is further divided into four phases.<sup>18,19</sup>

- Phase I : Period of no contraction.
- Phase II : Period of intermittent contraction.
- Phase III : Period of regular contractions at the maximal frequency that migrate distally.

Phase IV : Period of transition between phase III and phase I.

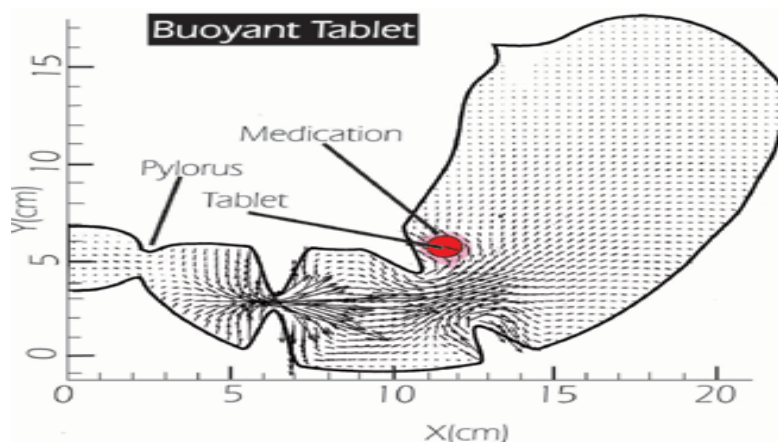
Phase III has a housekeeping role and serves to clear all indigestible materials from the stomach and small intestine. Consequently, a controlled-release gastrointestinal drug delivery system must be capable of resisting the house keeping action of phase III. Studies revealed that in the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. It can be concluded that feeding results in a lag time before onset of gastric emptying cycle.

### *Approaches to gastric retention*

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include –

#### *a) Floating Systems:*

*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. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems.



**Fig. 3 : Graphic of Buoyant tablet which is less dense than the stomach fluid and therefore remains in the fundus.**

#### *b) Bio/Muco-adhesive Systems:*

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

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

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.

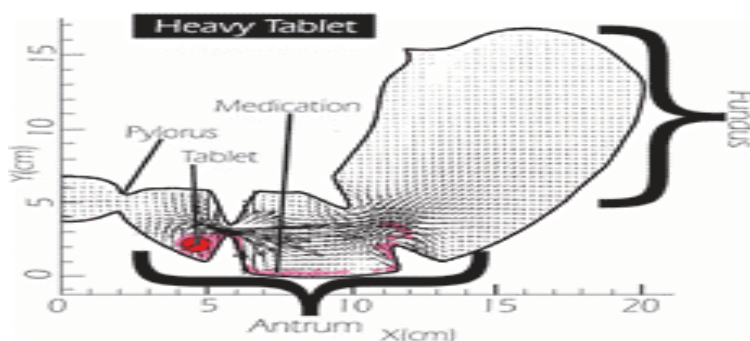
### ***c) Swelling and Expanding Systems:***

These are the dosage forms, which after swallowing, swell to 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 system*”, since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. 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.

A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

### ***d) High Density Systems:-***

These systems with a density of about  $3 \text{ g/cm}^3$  are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of  $2.6\text{-}2.8 \text{ g/cm}^3$  acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach as shown in Fig. 4.



**Fig. 4: Graphic of heavy tablet which is denser than the stomach fluid and therefore sinks to the antrum**

***e) Incorporation of Passage Delaying Food Agents:-***

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C<sub>10</sub>-C<sub>14</sub>.

***f) Ion Exchange Resins:***

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

***g) Osmotic Regulated Systems:***

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

**Types of floating drug delivery systems (FDDS)**

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are :

- A. Effervescent System, and
- B. Non- Effervescent System.

***A. Effervescent System:-***

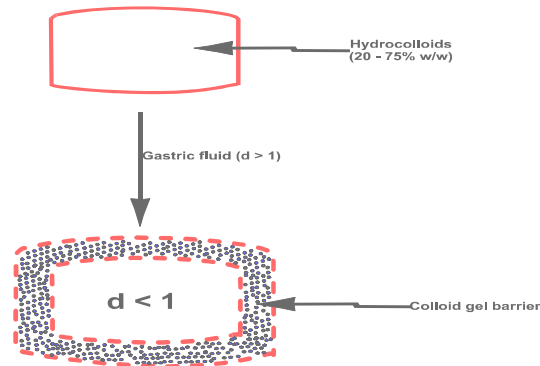
Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO<sub>2</sub>) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types.

- I. Gas Generating systems
- II. Volatile Liquid/Vacuum Containing Systems.

**I. Gas – Generating Systems:****1. Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS):**

These are as shown in Fig.5 and formulated by intimately mixing the CO<sub>2</sub> generating agents and the drug with in the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

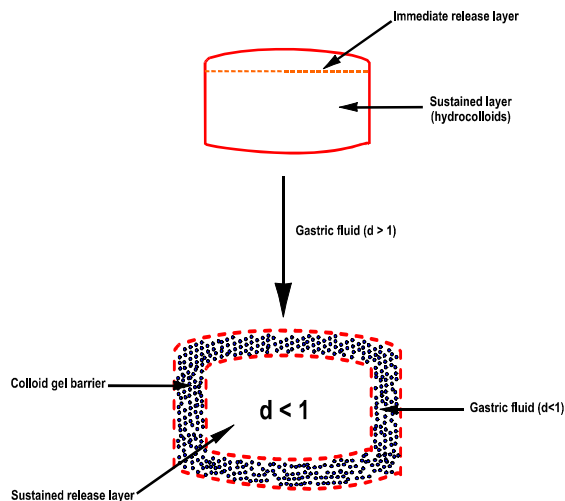


**Fig. 5 : Intra Gastric Single Layer Floating Tablet**

**2. Intra Gastric Bilayer Floating Tablets:**

These are also compressed tablet as shown in Fig 6 and containing two layer i.e.,

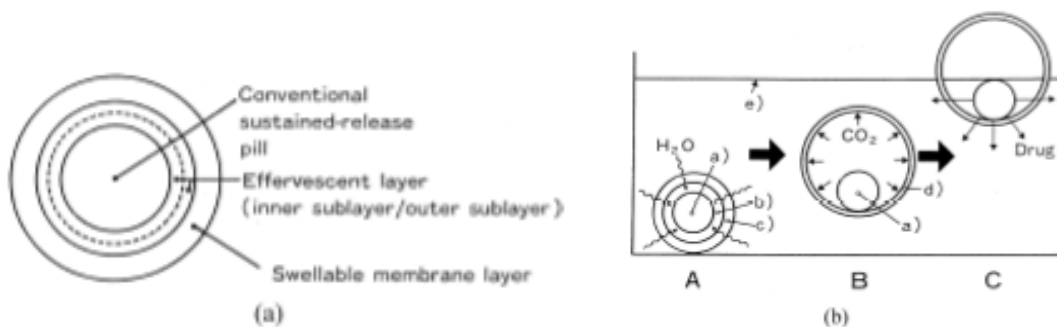
- i. Immediate release layer and
- ii. Sustained release layer.



**Fig. 6: Intra Gastric Bilayer Floating Tablet.**

### 3. Multiple Unit type floating pills:

These system consist of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consist of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO<sub>2</sub> within the system.

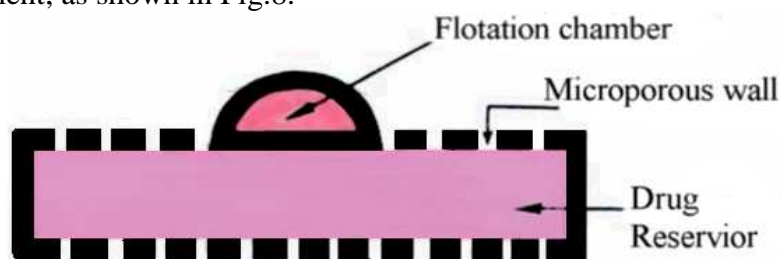


**Fig. 7 : (a) A multi-unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO<sub>2</sub> and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37<sup>0</sup>C).**

## II. Volatile Liquid / Vacuum Containing Systems:

### 1. Intra-gastric Floating Gastrointestinal Drug Delivery System:

These system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment, as shown in Fig.8.

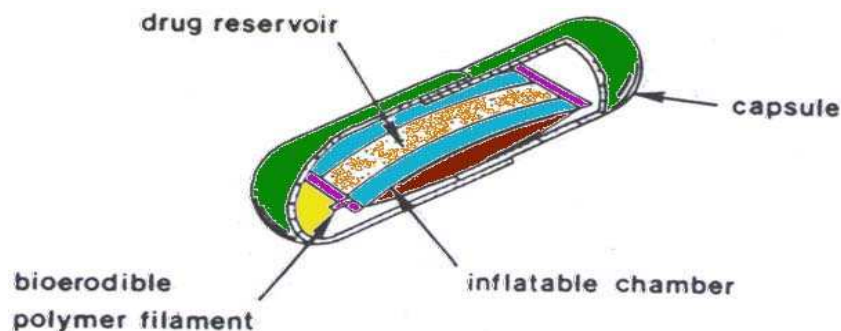


**Fig.8 : Intra Gastric Floating Gastrointestinal Drug Delivery Device**

### 2. Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule

dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid. This system is shown in Fig. 9.



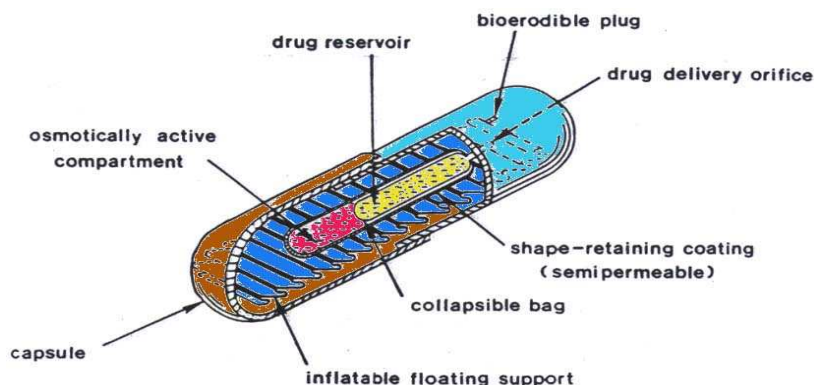
**Fig. 9: Inflatable Gastrointestinal Delivery System**

### ***3. Intra-gastric Osmotically Controlled Drug Delivery System:***

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in Fig. 10.



**Fig. 10: Intra-gastric Osmotically Controlled Drug Delivery System**

### **B. Non effervescent systems:**

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The various types of this system are as:

#### **1. Single Layer Floating Tablets:**

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

#### **2. Bilayer Floating Tablets:**

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

#### **3. Algininate Beads:**

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, these floating beads gave a prolonged residence time of more than 5.5 hour.

#### **4. Hollow Microspheres:**

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol:dichloromethane solution of

the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.

### ***Factors Controlling Gastric Retention Time of Dosage Form:***

The gastric retention time (GRT) of dosage form is controlled by several factors, that affect their efficacy as a gastroretentive system.

- Density – GRT is a function of dosage form buoyancy that is dependent on the density.
- Size – Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT.
- Shape of dosage form – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilopounds 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.<sup>32</sup>
- 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±0.6 hours) is less compared with their age and race-matched female counterparts (4.6±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.<sup>33</sup>
- Concomitant drug administration – Anticholinergics like Atropine and Propantheline, opiates like Codeine and prokinetic agents like Metoclopramide and Cisapride.
- Biological factors – Diabetes and Crohn's disease.

**List of Drugs along with Floatable Drug Delivery Systems:**

<b>SR. NO.</b>	<b>DOSAGE FORM</b>	<b>DRUGS</b>
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, 1-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

**Marketed Products of FDSS**

<b>SR. NO.</b>	<b>BRAND NAME</b>	<b>DRUG (DOSE)</b>	<b>COMPANY, COUNTRY</b>	<b>REMARKS</b>
1.	Modapar <sup>®</sup>	Levodopa (100 mg), Benserazide (25 mg)	Roche Products, USA	Floating CR capsule
2.	Valrelease <sup>®</sup>	Diazepam (15 mg)	Hoffmann-LaRoche, USA	Floating capsule
3.	Liquid Gavison <sup>®</sup>	Al hydroxide (95 mg), Mg carbonate (358 mg)	Glaxo Smith Kline, India	Effervescent floating liquid alginate preparation
4.	Topalkan <sup>®</sup>	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
5.	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDSS
6.	Cifran OD <sup>®</sup>	Ciprofloxacin (1 gm)	Ranbaxy, India	Gas-generating floating tablet
7.	Cytotec <sup>®</sup>	Misoprostal (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
8.	Oflin OD <sup>®</sup>	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet

## Conclusion

A novel floating controlled-release drug delivery system was formulated in an effort 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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