ABSTRACT

In recent years, scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as Gastroretentive systems, hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. The purpose of writing this review is to focus on the principal mechanism of floating to achieve gastric retention. This review involves classification, mechanism of floating, factors affecting FDDS, in-vitro and in-vivo techniques and applications of these systems.

KEYWORDS

FDDS, Single and Multiple Units, Evaluation Tests and Applications

INTRODUCTION

The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, patient compliance and flexibility in formulation, etc. During the past few decades, numerous oral drug delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a specific period of time at a predetermined and controlled rate. It is evident from the recent scientific and patent literatures that an increased interest in novel oral Controlled release dosage forms that designed to be retained in the gastrointestinal tract (GIT) for a prolonged and predictable period of time exist today. Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS).

Floating drug delivery systems (FDDS) are those systems which have a bulk density less than gastric fluids and because of this, these systems remains buoyant (3-4 hours) for a prolonged period of time in the stomach without affecting the gastric emptying rate. The drug is released slowly at the desired rate from the system and after release of the drug; the residual
system is emptied from the stomach. As a result, GRT is increased and fluctuations in plasma drug concentration can be better controlled.

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms that reside in the stomach for a longer period of time than conventional dosage forms.

A lot of scientific and technological advancements have been made in the drug delivery research in the recent years. Physiological problems like short Gastric Residence Time (GRT) and the unpredictable Gastric Emptying Time (GET) were overcome with the use of floating dosage forms which provide opportunity for both local and systemic drug action.

**Gastrointestinal Tract Physiology**

![Figure 1: Structure of Stomach](image)

Classification of Gastro Retentive Drug Delivery System

![Diagram](image)

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body 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. The proximal part made of fundus and body 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.

**Table 1: pH and Transit Time values GIT**

<table>
<thead>
<tr>
<th>pH</th>
<th>Values</th>
<th>Fluids</th>
<th>Solids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>1-3.5</td>
<td>50 Min</td>
<td>8 Hr</td>
</tr>
<tr>
<td>Duodenum</td>
<td>5-7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>6-7</td>
<td>2 – 6 Hr</td>
<td>4 – 9 Hr</td>
</tr>
<tr>
<td>Rectum</td>
<td>7</td>
<td>2 – 6 Hr</td>
<td>3 Hr – 3 Days</td>
</tr>
</tbody>
</table>
Gastric Emptying

Gastric emptying occurs during fasting as well as fed states\(^1\). The pattern of motility is however distinct in the 2 states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington:

**Phase I** (basal phase) lasts from 40 to 60 minutes with rare contractions.

**Phase II** (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

**Phase III** (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

**Phase IV** lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

[Image: Phases of gastric emptying]

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

Need for Gastro Retention

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

**Formulation Considerations for GRDDS**

- It must be effective retention in the stomach to suit for the clinical demand
- It must have sufficient drug loading capacity
- It must control the drug release profile
- It must have full degradation and evacuation of the system once the drug release is over
- It should not have effect on gastric motility including emptying pattern
- It should not have other local adverse effects.

**Drug Candidates Suitable For GRDDS**

- Drugs those are locally active in stomach. Eg: Misoprostal, Antacids
- Drugs with narrow absorption window in GIT. Eg: Furosemide, Riboflavin, L-DOPA
- Drugs those are unstable in intestinal or colonic fluids. Eg: Captopril, Metronidazole
Floating Drug Delivery System - A Review

- Drugs that kill the microbial flora in intestine. Eg: Antibiotics
- Drugs that has low solubility at high pH. Eg: Diazepam, Verapamil

**Drug Candidates not Suitable for GRDDS**

- Drugs with very limited acid solubility. Eg: Phenytoin
- Drugs those are instable in gastric environment
- Drugs that are intended for release in lower parts of GIT i.e. colon, rectum Eg: 5-amino salicylic acid, Corticosteroids

**Requirements for Gastric Retention**

From the discussion of the physiological factors in the stomach it must be noted that to achieve gastric retention, the dosage form must satisfy certain requirements.

One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must be resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

**Factors Affecting Floating Drug Delivery System**

The following factors affect the floating drug delivery systems in GIT.

**Density**

Density of the dosage form should be less than the gastric contents (1.004 gm/ml).

**Size and Shape**

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT for 90 to 100% retention at 24 hours compared with other shapes.

**Fed or Unfed State**

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (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 the Meal**

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

**Caloric Content**

GRT can be increased between 4 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 meals (3.4±0.4 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 years have a significantly longer GRT.

**Posture**

GRT can vary between supine and upright ambulatory states of the patients

**Concomitant Drug Administration**

Anticholinergic like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.
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.

Advantages of FDDS

- The Floating systems are advantageous for drugs meant for local action in the stomach. E.g. antacids.
- Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
- The Floating systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
- Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents.
- It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

Disadvantages of FDDS

- Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.
- The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

Floating Drug Delivery System

The concept of FDDS was described in the literature as early as 1962. Floating drug delivery system is also called as hydro dynamically balanced system (HBS). It has a bulk density which is less than the gastric contents and hence remains buoyant in the stomach for a prolonged period of time 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 the desired rate from the system. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The device must have sufficient structure to form a cohesive gel barrier, it must maintain an overall specific gravity lower than that of gastric contents (1.004-1.010) and it should dissolve slowly enough to serve as a drug reservoir. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.

Table 2: Types of different buoyant forms

<table>
<thead>
<tr>
<th>Dosage Forms</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td>Chlrorpheniramine, Theophylline, Furosemide, Ciprofloxaci, Captopril, Acetylsalicylic acid, Amoxycillin trihydrate, Verapamil HCl, Isosorbide dinitrate, Isosorbide mononitrate, Acetaminophen, Ampicillin, Cinnarazine, Diltiazem, Florouracil, Prednisolone,</td>
</tr>
<tr>
<td>Capsules</td>
<td>Nicardipine, Chlordiazepoxide HCl, Furosemide, Misoprostal, Diazepam, Propranal Urodeoxycholic acid.</td>
</tr>
<tr>
<td>Microsperes</td>
<td>Aspirin, Griseofulvin, and p-nitroaniline, Ketoprofen, Iboprunef, Terfenadine</td>
</tr>
<tr>
<td>Granules</td>
<td>Indomethacin, Diclofenac sodium, Prednisolone</td>
</tr>
</tbody>
</table>
Mechanism of Floating Systems

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing 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. Among these, the floating dosage forms have been most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so 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 (given in the Figure 3, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Figure 3). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

\[ F = F_{buoyancy} - F_{gravity} = (D_f - D_s) g v \quad (1) \]

Where, \( F \) = total vertical force, \( D_f \) = fluid density,

\( D_s \) = object density, \( v \) = volume and \( g \) = acceleration due to gravity.

Types of Floating Drug Delivery Systems

Based on the mechanism of buoyancy and two distinctly different technologies have been utilized in the development of FDDS.

1) Non-Effervescent FDDS
2) Effervescent FDDS

Non-Effervescent FDDS

The Non-effervescent FDDS is 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, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol.

Figure 3: Mechanism of Floating Systems, GF= Gastric fluid

Figure 4: HBS Capsule
The various types of this system are as:

A. **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 maintains bulk density of less than unity\(^7\). They are formulated by intimate mixing of drug with low-density enteric materials such as CAP, HPMC.

B. **Bi-layer Floating Tablets**

A bi-layer tablet contains two layers; one immediate release layer which releases initial dose from the system while the other 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.

C. **Alginate 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 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\(^8\). When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

D. **Hollow Microspheres**

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40\(^\circ\)C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.

![Figure 5: Bilayer Floating Tablet](image5.png)

![Figure 6: Hollow Microspheres](image6.png)

**Effervescent System**

Effervescent systems include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. Citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO\(_2\)) gas, thus reducing the density of the system and making it float on the gastric fluid\(^9\). An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature. These effervescent systems further classified into two types.

A. Gas generating systems

B. Volatile liquid/vacuum containing systems
Gas Generating Systems

Tablets

Floating bilayer tablets with controlled release for furosemide were developed by. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio. One layer contained the polymers HPMC K4M, HPMC K100M and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid.

The in-vitro floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, i.e., when the tablets were compressed at 15 MPa, these could begin to float at 20 minutes whereas at a force of 32 MPa the time was prolonged to 45 minutes.

Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets.

On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.

Floating Capsules

Floating capsules are prepared by filling with a mixture of sodium alginate and sodium bicarbonate. The systems were shown to float during in vitro tests as a result of the generation of CO₂ that was trapped in the hydrating gel network on exposure to an acidic environment.

Multiple Unit Type Floating Pills

The system consists of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swell able 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 CO₂ within the system.

Floating System with Ion-Exchange Resins

A floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1M sodium bicarbonate solution. The loaded beads were then surrounded by a semipermeable membrane to avoid sudden loss of CO₂. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO₂ generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. The in-vivo behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours).
Volatile Liquid / Vacuum Containing Systems

**Intra-gastric Floating Gastrointestinal Drug Delivery System**

These systems 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 micro-porous compartment.

![Figure 9: Intragastric Floating GDDS](image)

**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, 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.

![Figure 10: Inflatable GDDS](image)

**Intragastric 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.

The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release 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.

![Figure 11: Intragastric Osmotically Controlled Drug Delivery System](image)
Other Types of Gastroretentive Systems

Bioadhesive Drug Delivery System

The term bioadhesion is defined as adhesion to biological surface i.e. Mucus and/or mucosal surface. In instances when the polymeric system interacts with mucus layer only, it is referred as mucoadhesion. In order to develop an ideal oral bioadhesive system, it is important to have a thorough understanding of mucosa, bioadhesive polymers and mucin-polymer interactions in the physiological environment. Intestinal mucosa is composed of high molecular weight glycoproteins hydrated and covering the mucosa with a continuous adherent blanket. Mucin glycoproteins are rich with fucose and sialic acid groups at the terminal ends which provide a net negative charge in the acidic environment. The thickness of the mucin gel layer varies in different regions of the GIT with thickness ranging between 50-500 µm in stomach to 15-150µm in the colon. Cohesion of the mucin gel is dependent upon the glycoprotein concentration. The mucus layer is created biologically to play a number of important functions of protecting the underlying tissues from various diffusing/corrosive elements such as enzymes, acid and other toxic molecules. Also being a visco-elastic gel, it helps in the passage of food over the epithelium, thereby minimizing potential erosive damages. The mucus layer, in addition to providing protection, provides a barrier to drug absorption. Various investigators have proposed different mucin-polymer interactions, such as Wetting and swelling of the polymer to permit intimate contact with the biological tissue. Interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin chains. Formation of weak chemical bonds sufficient polymer mobility to allow spreading Water transport followed by mucosal dehydration.

As the mucus layer comes into contact with bioadhesive coated system, various non-specific (Vander Waals, hydrogen bonding and/or hydrophobic interactions) or specific interactions occur between the complimentary structures. However, these interactions last only until the turnover process of mucin and, in order for a bioadhesive system to be successful; it should release its drug contents during this limited adhesion time.

Raft-Forming Systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO₂ bubbles on contact with gastric fluid.

Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastro esophageal reflux treatment as with liquid gaviscon.

High Density Systems

Gastric contents have a density close to water (1.004 g /cm³). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g/cm seems necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.

Low Density Systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1 g/cm3) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called “microballoons” because of the low-density core. Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion methods. Polycarbonate, Eudragit S, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers.
Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the solvent used.

**Expandable Systems**

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required, a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release. Unfoldable systems are made of biodegradable polymer; the concept is to make a carrier, such as a capsule, incorporating a compressed system, which extends in the stomach. Proposed different geometric forms (tetrahedron, ring or planar membrane (4-lobed, disc or 4-limbed cross form) of biodegradable polymer compressed within a capsule.

**Swellable System**

Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids, the bulk enable gastric retention and maintains the stomach in a ‘fed’ state, suppressing housekeeper waves.

**Superporous Hydrogels**

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification (Chen and park, 2000) with pore size ranging between 10 nm and 10 µm. Absorption of water by conventional hydrogel is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Superporous hydrogel, average pore size > 100 µm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover they swell to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co- formulation of a hydrophilic particulate material, Ac-DiSol (cross carmellose sodium).

**Magnetic System**

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach. Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision. Probably, the development of new conveniently applied magnetic field sources will improve this concept.

**Self-Unfolding Systems**

The self-unfolding systems are capable of mechanically increasing in size relative to the initial dimensions. This increase prevents the system from passing via the pylorus and provides for its prolonged stay in the stomach. A drug can be either contained in a polymeric composition of the gastroretentive system or included as a separate component. Several methods were suggested to provide for the self-unfolding effect.

- The use of hydrogels swelling in contact with the gastric juice.
- Osmotic systems, comprising an osmotic medium in a semi-permeable membrane.
- Systems based on low-boiling liquids converting into a gas at the body temperature.

**Formulation Aspects**

The design of novel controlled release dosage forms should take into account three important, criteria, viz., drug, delivery, and destination.
Excipients Used In FDDS
Following types of ingredients can be incorporated into HBS dosage form in addition to the drugs.

![Types of Gastroretentive Drug Delivery Systems](image)

**Hydrocolloids**
(20%-75%). They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. Eg. Acacia, pectin, Chitosan, agar, casein, bentonite, veegum, HPMC (K4M, K100M and K15M), Gellangum (Gelrite®).

**Inert Fatty Materials**
(5%-75%) Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. Eg. Beeswax, fatty acids, and long chain fatty alcohols.

**Effervescent Agents**
Sodium bicarbonate, citric acid, tartaric acid, DiSGC (Di-Sodium Glycine Carbonate), CG (Citroglycine).

**Disintegrating Agents**
Povidone, Polyplasdone XL and XL-10

**Viscolyzing Agents**
Sodium alginate, Carbopol 934

**Release Rate Accelerants**
(5%-60%). eg lactose, mannitol

**Release Rate Retardants**
(5%-60%): Dicalcium phosphate, talc, magnesium stearate

**Buoyancy Increasing Agents**
(upto80%): eg. EthylCellulose

**Low Density Material**
Polypropylene foam powder (Accurel MP 1000®).

**Evaluation of Floating Drug Delivery Systems**

**Pre-compression Parameters**

a) **Angle of Repose**
The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

\[ \tan \Theta = \frac{h}{r} \]
\[ \Theta = \tan^{-1} \left( \frac{h}{r} \right) \]

Where, \( \Theta \) = angle of repose, \( h \) = height of the heap, \( r \) = radius of the heap

Table 3: Relationship between Angle of Repose and Powder Flow

<table>
<thead>
<tr>
<th>Angle of repose</th>
<th>Powder flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>Excellnt</td>
</tr>
<tr>
<td>25-30</td>
<td>Good</td>
</tr>
<tr>
<td>30-40</td>
<td>Passable</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>Very poor</td>
</tr>
</tbody>
</table>
b) Compressibility Index

The flowability of powder can be evaluated by comparing the bulk density ($\rho_\text{b}$) and tapped density ($\rho_\text{t}$) of powder and the rate at which it packed down. Compressibility index was calculated by:

$$\text{Compressibility index} (\%) = \frac{\rho_\text{t} - \rho_\text{b}}{\rho_\text{t}} \times 100$$

Where $\rho_\text{b}$ = Bulk density g/cc, $\rho_\text{t}$ = Tapped density g/cc

Post-compression Parameters

a) Shape of Tablets

Compressed tablets were examined under the magnifying lens for the shape of the tablet.

b) Tablet Dimensions

Thickness and diameter were measured using a calibrated Vernier caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

c) Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester.

It was expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets was determined.

d) Friability test

The friability of tablets was determined by using Roche Friabilator. It was expressed in percentage (%). Ten tablets were initially weighed ($W_{\text{initial}}$) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again ($W_{\text{final}}$). The % friability was then calculated by

$$\% F = 100 (1 - \frac{W_{\text{final}}}{W_{\text{initial}}})$$

% Friability of tablets less than 1% was considered acceptable.

e) Tablet Density

Tablet density was an important parameter for floating tablets. The tablet would floats only when its density was less than that of gastric fluid (1.004). The density was determined using following relationship.

$$V = \pi r^2 h$$

$d = \frac{m}{v}, \quad v = \text{volume of tablet (cc)}, r = \text{radius of tablet (cm)}$

$h = \text{crown thickness of tablet (g/cc)}, m = \text{mass of tablet}$

f) Specific Gravity

Specific Gravity of the floating system can be determined by the displacement method using benzene as a displacing medium

g) Weight Variation Test

Ten tablets were selected randomly from each batch and weighed individually to check for weight initial variation. A little variation was allowed in the weight of a tablet by U.S. Pharmacopoeia. The following percentage deviation in weight variation was allowed show in table 4.

<table>
<thead>
<tr>
<th>Average weight of a tablet</th>
<th>Percent deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>130mg or less</td>
<td>10</td>
</tr>
<tr>
<td>&gt;130mg and &lt;324mg</td>
<td>7.5</td>
</tr>
<tr>
<td>324 mg or more</td>
<td>5</td>
</tr>
</tbody>
</table>

h) Buoyancy / Floating Test

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

i) Swelling Study

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be
measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.

\[ WU = \frac{W_t - W_0}{W_0} \times 100 \]

Where, \( W_t \) = Weight of dosage form at time \( t \).
\( W_0 \) = Initial weight of dosage form.

**j) In-vitro Dissolution Study**

Dissolution tests are performed using USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium; replenished with the same volume of fresh medium at sampling time points. Recent methodology as described in the USP XXIII states “the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of non-reactive material such as not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float”. However, standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors of in-vitro performance for floating dosage forms.

**k) Drug Release**

Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

**l) X-Ray/Gamma Scintigraphy**

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form now a day. It helps to locate dosage form in the GIT and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a \( \gamma \)-emitting radionuclide in a formulation allows indirect external observation using a \( \gamma \)-camera or scintiscanner. In case of \( \gamma \)-scintigraphy, the \( \gamma \)-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract.

**m) Pharmacokinetic Studies**

Pharmacokinetic studies are the integral part of the \textit{in vivo} studies and several works has been on that. Sawicki studied the pharmacokinetics of verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40mg). The \( t_{\text{max}} \) and AUC (0-infinity) values (3.75 h and 364.65 ng.ml-1h respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (\( t_{\text{max}} \) value 1.21 h, and AUC value 224.22 ng.ml1h). No much difference was found between the Cmax values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. An improvement in bioavailability has also been observed with piroxicam in hollow polycarbonate microspheres administered in rabbits. The microspheres showed about 1.4 times more bioavailability, and the elimination half-life was increased by about three times than the free drug.

**n) Drug-Excipient (DE) Interactions**

This is done using FTIR. Appearance of a new peak, and/or disappearance of original drug or excipient peak indicate the DE interaction. Apart from the above mentioned evaluation parameters, granules (ex: Gelucire 43/01) are also evaluated for the effect of ageing with the help of Differential Scanning Calorimeter or Hot stage polarizing microscopy.

**Application of Floating Drug Delivery System**

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follow:

**Sustained Drug Delivery:** Eg. Sustained release floating capsules of nicardipine.
**Floating Drug Delivery System - A Review**

**Site-Specific Drug Delivery:** Eg. Furosemide monolithic floating dosage.

**Absorption Enhancement:** Eg. A significantly increase in the bioavailability of floating dosage forms(42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).

Table 5: Marketed Products of Floating Drug Delivery Systems

<table>
<thead>
<tr>
<th>Name</th>
<th>Type and Drug</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MadoparHBS (PropHBS)</td>
<td>Floating capsule, Levodopa and benserazide</td>
<td>Floating CR capsules</td>
</tr>
<tr>
<td>Valrelease</td>
<td>Floating capsule, Diazepam</td>
<td>Floating Capsules</td>
</tr>
<tr>
<td>Topalkan</td>
<td>Floating Antacid, aluminium and magnesium mixture</td>
<td>Effervescent floating liquid alginite preparation</td>
</tr>
<tr>
<td>Amalgate Float Coat</td>
<td>Floating Antacid, Floating gel,</td>
<td>Floating dosage form</td>
</tr>
<tr>
<td></td>
<td>Colloidal gel forming FDDS</td>
<td></td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Colloidal gel floating FDDS</td>
</tr>
<tr>
<td>Cifran OD</td>
<td>Ciprofloxacin (1 gm)</td>
<td>Gas generating floating form</td>
</tr>
<tr>
<td>Cytotech</td>
<td>Misoprostol (100 mcg/200 mcg)</td>
<td>Bilayer floating capsule</td>
</tr>
<tr>
<td>Liquid Gaviscone</td>
<td>Mixture of alginite</td>
<td>Suppress gastro esophageal</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Gastroretentive drug delivery systems have emerged as a 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, magnetic, and high density systems. 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, formulation strategies, and correct combination of drug and excipients.

**REFERENCES**


© Copyright reserved by IJPRS Impact Factor = 1.0285


