Floating Drug Delivery System: A Novel Approach towards Gastro retention


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ABSTRACT
Conventional pharmaceutical dosage forms with narrow absorption window in the gastrointestinal tract have poor absorption. Therefore, gastroretentive drug delivery systems (GRDDS) have been developed, which offer the advantages in prolonging the gastric emptying time. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. Several techniques such as floating drug delivery system, low density systems, raft systems, mucoadhesive systems, high density systems, superporous hydrogels and magnetic systems, have been employed. Among these systems, FDSS have been most commonly used. This article provides the entire classification of floating drug delivery systems, factors affecting gastroretensive systems, advantages and disadvantages of floating drug delivery systems and a comparative diagrammatic representation limelight this article.

Keywords: Gastroretentive drug delivery systems, Floating tablet, effervescent, noneffervescent.

INTRODUCTION
The oral route is considered as the most promising route of drug delivery. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day. Recently, Novel drug delivery systems that could revolutionize method of medication and provide a number of therapeutic benefits. The development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in systemic circulation for a long time. These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine). Drugs that have narrow absorption window in the GIT will have poor absorption. For these drugs, gastroretentive drug delivery systems offer the advantages in prolonging the gastric emptying time. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density systems, low density systems, bioadhesion systems, unfoldable, swellable systems, superporous hydrogel systems, magnetic systems etc.
BASIC PHYSIOLOGY OF STOMACH

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.

Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted states. Furthermore, the relative brief gastric emptying time in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose.

Normal gastric residence times usually range between 5 minutes to 2 h.

During the fasting state an interdigestive 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:

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. 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.
3. 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.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.
GASTRORETENTIVE DRUG DELIVERY SYSTEMS (GRDDS)

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. If the drugs are poorly soluble in the intestine due to alkaline pH, gastric retention may increase solubility before they are emptied.

The drug candidates having “absorption window” in a particular region of GI tract are difficult to be designed as oral CRDDS. This is because only the drug released in the region preceding the ‘window’ vicinity of “absorption window” is available for absorption. The GRDDS releasing the drug prior to “absorption window”, for prolonged period of time & thus ensuring optimal absorption.¹⁹

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**Fig. 2:** Pictorial representation of the typical motility patterns in the fasting state

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**Fig. 3a:** Conventional dosage form system²⁰

**Fig. 3b:** Gastroretentive drug delivery¹⁹
APPROACHES TO GASTRIC RETENTION

1) **Bioadhesive approach**: In which the adhesive capacity of some polymer with glycoprotein is closely applied to the epithelial surface of the stomach.\(^{21}\)

2) **High density approach**: The density of the pellets should be higher than the stomach fluid. It would be at least 1.50 g/ml. In this type, the drug can be coated or mixed with heavy, nontoxic materials such as barium sulfate, titanium dioxide, etc.\(^5\)

3) **Low density approach**: In this approach, the density of pellets should be less than 1 g/ml, so as to float the pellets or tablets in the gastric fluid and, release the drug slowly for a longer period of time.\(^5\)

4) **Swelling approach**: After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus. These systems are sometimes referred to as plug type systems because they tend to remain loaded at the pyloric sphincter.\(^{20}\)

5) **Magnetic systems**: This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. Ito et al. used this technique in rabbits with bioadhesives granules containing ultrafine ferrite (g-Fe2O3). They guided them to the oesophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 h.\(^{22}\) Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.\(^{17,23}\)

**FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORM**: \(^{24,25,26}\)

The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include:

1) **Density of dosage forms**
   Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm\(^3\) is required to exhibit floating property.\(^{18}\)

2) **Shape and size of the dosage form**
   In most cases, the larger the dosage form the greater will be the
gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.19

3) Food intake and its nature
Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the GIT influences the GRT of the dosage form. Usually the presence of food in the GIT improves the GRT of the dosage form. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms.24

4) 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.15

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

6) 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.

7) 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.

8) Age
Elderly people, especially those over 70, have a significantly longer GRT.

9) Posture
GRT can vary between supine and upright ambulatory states of the patient.18

10) pH
The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn’t get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state.15

11) Volume
The resting volume of the stomach is 25 to 50 ml. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is Faster.15,18

FLOATING DRUG DELIVERY SYSTEMS (FDDS) AND ITS MECHANISM
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.27 While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system.28 After release of drug, the residual system is emptied from the stomach. 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 (RW) has been reported in the literature. The RW 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 RW is on the higher positive side. This apparatus helps in optimising FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

\[ \text{RW} = F_{\text{buoyancy}} - F_{\text{gravity}} = (D_f - D_s) g V, \]

Where: \( \text{RW} = \) total vertical force, \( D_f = \) fluid density, \( D_s = \) object density, \( V = \) volume and \( g = \) acceleration due to gravity.

**ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM (FDDS)**

1) FDDS are advantageous for drugs meant for local action in the stomach, e.g., Antacids.
2) FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in the stomach to get a relatively better response.
3) Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
4) Certain types of drugs can benefit from using FDDS. These include:
   a) Drugs those are primarily absorbed in the stomach.
   b) Drugs those are poorly soluble at an alkaline pH.
   c) Drugs with a narrow window of absorption.
   d) Drugs absorbed rapidly from the GI tract.
   e) Drugs those degrade in the colon.
DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM (FDDS)\textsuperscript{17}

1) 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) Drugs that are unstable in its acidic environment should not be formulated in gastroretentive systems.

3) Drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract, drugs undergoing first pass metabolism will not benefit from incorporation into a gastric retention system.

4) It requires sufficient high level of the fluids in the stomach for the drug delivery to float. However, this can be overcome by administering the dosage form with a glass full of water (200-250 ml) with frequent meals.

5) Also single unit floating capsules or tablets are associated with an “all or none concept,” but this can be overcome by formulating multiple unit systems like floating microspheres or microballoons.

CLASSIFICATION OF GASTRORENTENTIVE DRUG DELIVERY SYSTEM\textsuperscript{19,29}

A) Effervescent systems

1) Gas – Generating Systems

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\textsubscript{2}) gas\textsuperscript{30}, 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. A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas. The gas in floating chamber can be introduced either by the volatilisation of the organic solvent or by the effervescent reaction between organic acids and bicarbonate salts.\textsuperscript{19}

1) Gas – Generating Systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO\textsubscript{2}, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{gasGeneratingSystem.png}
\caption{Gas Generating System\textsuperscript{28}}
\end{figure}
The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach. Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

Kumar et al formulated the floating matrix tablets of acyclovir using swellable polymers like HPMC K4M, HPMC K15M and sodium alginate with NaHCO₃ as effervescent agent. Mallikarjun et al developed a floating tablets of Glipizide by effervescent technique; polymers were evaluated for their gel forming properties, NaHCO₃ incorporated as effervescent agent. Yadav et al developed floating-bioadhesive bilayer tablet(propranolol HCl). Meka et al had developed a gastro retentive FDDS with multiple-unit minitab’s based on gas formation technique,(Captoril).

2) Volatile Liquid / Vacuum Containing Systems
a) 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.

b) 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 consist 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 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.

Fig. 8: Intragastric Osmotically Controlled Drug Delivery System

B) Non effervescent systems
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. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain the relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped the swollen polymer confirms buoyancy to these dosage forms. This systems can be further divided into the subtypes:

1) Algnate 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. The beads are then separated, snap-frozen in the liquid nitrogen, and freeze-dried at -40°C for 24 hours, 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.
Shimpi et al formulated a multiple a multi unit floating granules of diltiazem hydrochloride using gelucire 43/01.\(^{38}\)

2) Hollow Microspheres
Hollow microspheres are considered as one of the most promising buoyant systems, as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere\(^ {17}\). The general techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. Polycarbonate, Eudragit S, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers in preparation of hollow microsphere.

Buoyancy and drug release are dependent on quantity of polymer, the plasticizer-polymer ratio and the solvent used\(^ {39,40}\). 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.

![Fig. 9: Preparation technique (emulsion-solvent diffusion method) and mechanism of ‘microballoon’ formation proposed by Kawashima et al.\(^ {41}\)](image)

![Fig. 10: Micro balloons\(^ {17}\)](image)
3) Colloidal gel barrier systems / Hydrodynamically balance system
Hydrodynamically balance system (HBS™) was first design by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This systems incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids. e.g. HEC, HPMC, Polysaccharides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms.

Fig. 11: Schematic diagram shows the mode of action for HBS(Bogentoft,1982)

4) Microporous Compartment System
This technology is based on the encapsulation of drug reservoir inside a Microporous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.

Fig. 12: Intra Gastric Floating Gastrointestinal Drug Delivery Device
EVALUATION OF FLOATING TABLETS

1) Floating/buoyancy lag time
It is the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.\textsuperscript{17,44}

2) Floating time
The test for floating time is usually performed in simulated gastric fluid maintained at 37$^\circ$C, by using USP dissolution apparatus containing 900 ml of 0.1 N HCl as the dissolution medium. The time for which the dosage form floats is termed as the floating or flotation time.\textsuperscript{17,44}

3) Dissolution study (floating)

Fig.13: In vitro dissolution method\textsuperscript{17}

Recently Gohel et al proposed a more relevant in vitro dissolution method to evaluate a floating drug delivery system (for tablet dosage form). A 100-mL glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 ml of 0.1 mole.lit-1 HCl dissolution medium and allow collection of samples. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic gastric acid secretion rate. The tablet did not stick to the agitating device in the proposed dissolution method. The drug release followed zero-order kinetics in the proposed method. Similarity of dissolution curves was observed between the USP method and the proposed method at 10% difference level ($f_2=57$). The proposed test may show good in vitro-in vivo correlation since an attempt is made to mimic the in vivo conditions such as gastric volume, gastric emptying, and gastric acid secretion rate.\textsuperscript{17}

4) 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.

5) Water uptake study
- The swelling of the polymers can be measured by their ability to absorb water and swell.
- Water uptake study of the tablet is performed using USP dissolution apparatus Type II.
- The medium used - distilled water, 500 ml rotated at 50 rpm and maintained at 37 $\pm$ 0.5 $^\circ$C, throughout the study.
- After selected time intervals, the tablets are withdrawn, blotted to remove excess water and weighed.

\[ \text{WU(96)} = \frac{\text{Weight of swollen tablet - Initial weight of the tablet}}{\text{Initial weight of the tablet}} \]

6) Content uniformity, Hardness, Friability (Tablets)
These tests are performed as per described in specified monographs.

7) X-Ray/Gamma Scintigraphy\textsuperscript{17}
- 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.\textsuperscript{17}
- 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 radionucleide in a formulation allows indirect external observation using a $\gamma$-camera or scintiscanner.
CONCLUSION
Recently many drugs have been formulated as floating drug delivery systems with an objective of sustained release and restricting the region of drug release to stomach. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The currently available polymer-mediated non-effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. The most important criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half life.

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