FLOATING DRUG DELIVERY SYSTEM: A REVIEW

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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). Systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the studies to evaluate the performance and application of floating systems, and applications of these systems. In this review, the current technological developments of FDDS including patented delivery systems and marketed products, and their advantages and future potential for oral controlled drug delivery are discussed.

KEYWORDS: Gastroretentive system, Intragastric floating systems; Hydrodynamically balanced systems, evaluation, scintigraphy.

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing
interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. 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. There are many difficulties faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying play a major role. 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. Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

**Basic Gastrointestinal Tract Physiology**

Basically 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, the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. 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 inter-digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases.
Phase I (basal phase) - lasts from 40 to 60 minutes with rare contractions.

Phase II (pre-burst 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. 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.

FLOATING DRUG DELIVERY SYSTEMS
Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine. This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from
the system. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration.

**The major requirements for floating drug delivery system are.**

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).
- It must form a cohesive gel barrier.

The inherent low density can be provided by the Entrapment of air (e.g. Hollow chambers) or by the incorporation of low density materials (e.g. Fatty materials or oils, or foam powder). These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems.

**CLASSIFICATION OF DRUG DELIVERY SYSTEM**

A. Single Unit Floating Dosage Systems
   a) Effervescent Systems (Gas-generating Systems)
   b) Non-effervescent Systems

B. Multiple Unit Floating Dosage Systems
   a) Non-effervescent Systems
   b) Effervescent Systems (Gas-generating Systems)
   c) Hollow Microspheres

C. Raft Forming Systems

**A) Single unit system**

Recently a single-unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler. The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produce irritation. On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce the inter- and intra- subject availabilities in drug absorption as well as to lower the possibility of dose dumping. Various multiple-unit floating system like air compartment multiple-unit system, hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method, microparticles based on low density foam powder, beads
prepared by emulsion gelatin method etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery system.

- **Non-effervescent systems**
  One or more gel forming, highly swellable, cellulosic hydrocolloids (e.g. hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxypropyl methyl cellulose [HPMC] and sodium carboxy methyl cellulose), polysaccharides, or matrix forming polymers(e.g.,polycarbophil, polyacrylates, and polystyrene) are incorporated in high level (20-75% w/w) to tablets or capsules. For the preparation of these types of systems, the drug and the gel forming hydrocolloid are mixed thoroughly. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

- **Effervescent systems or gas generating systems**
  These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO₂ is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.

![Fig.2. Swelling and gas generating systems](image-url)
B) Multiple Unit System

Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple unit systems avoid the ‘all-or-none’ gastric emptying nature of single unit systems. It reduces the intersubject variability in absorption and the probability for dose dumping is lower.

- **Non-effervescent systems**

A little or no much report was found in the literature on noneffervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates float in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

- **Effervescent systems**

A multiple unit system comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment was prepared. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads. Sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behavior of radiolabeled floating beads and compared with nonfloating beads in human volunteers using gamma scintigraphy. Prolonged gastric residence time of more than 5.5 h was observed for floating beads. The nonfloating beads had a shorter residence time with a mean onset emptying time of 1 hr.

- **Floating Microspheres**

A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres.
Techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers, such as polycarbonate, Eudragit® S and cellulose acetate, are used in the preparation of hollow microspheres, and the drug release can be modified by optimizing the amount of polymer and the polymer plasticizer ratio.

C) Raft Forming Systems
The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO2 and act as a barrier to prevent the reflux of gastric Contents like HCl and enzymes into the esophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of to make the system less dense and float on the gastric fluids.

ADVANTAGES OF FLOATING DOSAGE FORM
(1) These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.
(2) The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.
(3) The efficacy of the medicaments administered utilizing the sustained release principle of floating formulation has been found to be independent of the site of particular medicaments.
(4) Complete absorption of the drug from the floating dosage form is expected even at the alkaline pH of the intestine. The dissolution of the drug in gastric fluid occurs and then the dissolved drug is available for absorption in the small intestine after emptying of the stomach contents.
(5) Poor absorption is expected when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhoea. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
(6) Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant 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%).

LIMITATIONS OF FLOATING DRUG DELIVERY SYSTEMS

(1) A high level of fluid in the stomach is required for drug delivery to float and work efficiently.

(2) Drugs which have stability and solubility problems in GIT are not suitable candidates for these types of systems.

(3) Drugs such as nifedipine, which undergoes first pass metabolism may not be desirable for the preparation of these types of systems.

4) Drugs which are irritant to Gastric mucosa are also not desirable.

(5) The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.

EVALUATION PARAMETERS OF FDDS

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro floating behavior show prolonged gastric residence in vivo. Although, in vitro floating behavior alone is not sufficient proof for efficient gastric retention so in vivo studies can provide definite proof that prolonged gastric residence is obtained.

1) Weight variation

Uniformity of Weight according to Indian pharmacopoeia, 20 tablets were selected at random, weight together and individually for the determination of weight of tablets. The mean and standard deviations were calculated.

2) Hardness

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric Compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm2.

3) Thickness

Thickness and diameter of ten tablets were measured using vernier calipers.
4) Friability
Friability The friability test was carried out in Roch Friabilator. Ten tablets were weighted (Wo).

5) Floating lag time and total floating time determination
The time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. These tests are usually performed in simulated gastric fluid or 0.1 mole.lit-1 HCl maintained at 37o C, by using USP dissolution apparatus containing 900 ml of 0.1 molar HCl as the dissolution medium.

6) Drug release
The test for in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37 C. Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replaced with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started. A small, loose piece of non reactive material such as not more than a few turns of wire helix may be attached to the dosage units that would otherwise float. However, standard dissolution methods based on USP, British Pharmacopoeia (BP) have been shown to be poor predictors of in vitro performance for floating dosage forms.

7) Drug loading, drug entrapment efficiency, particle size analysis, surface characterization, micromeritics studies and percentage yield (for floating microspheres and beads)
Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. The particle size and the size distribution of beads or microspheres are determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM). The measured weight of prepared microspheres was divided by total...
amount of all non-volatile components used for the preparation of microspheres, which will give the total percentage yield of floating microspheres.

8) Resultant weight determination
Bulk density and floating duration have been the main parameters to describe the adequacy of a dosage form’s buoyancy. Although single density determination does not predict the floating force evolution of the dosage form because the dry material of it is made progressively reacts or interacts with in the gastric fluid to release its drug contents. So to calculate real floating capabilities of dosage form as a function of time a novel method has been conceived. It operates by force equivalent to the force F required to keep the object totally submerged in the fluid. This force determines the resultant weight of the object when immersed and may be used to quantify its floating or non-floating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the Victoria sum of buoyancy (Fbuoy) and gravity (Fgrav) forces acting on the objects as shown in the equation.

\[ F = F_{buoy} - F_{grav} \]
\[ F = d_f g V - d_s g V = (d_f - d_s) g V \]
\[ F = (d_f - M/V) g V \]

In which,
- \( F \) is total vertical force (resultant weight of the object),
- \( g \) is the acceleration due to gravity,
- \( d_f \) if the fluid density,
- \( d_s \) is the object density is the object mass and
- \( V \) is the volume of the object.

9) Weight gain and water uptake (WU)
Weight gain or water uptake can be studied by considering the swelling behavior of Floating dosage form. The study is done by immersing the dosage form in simulated gastric fluid at 37 C and determining the dimensional changes like tablet diameter and/ or thickness at regular 1-h time intervals until 24 h, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then reweighed and WU is measured in the terms of percent weight gain, as given by equation

\[ WU = \frac{(W_t - W_o) X 100}{W_o} \]

In which \( W_t \) and \( W_o \) are the weights of the dosage form at time \( t \) and initially, respectively.
10) XRay/ Gamma scintigraphy
For in vivo studies, X-Ray/Gamma Scintigraphy is the main evaluation parameter for floating dosage form. In each experiment, the animals are allowed to fast overnight with free access to water, and a radiograph is made just before the administration of the floating tablet to ensure the absence of radio-opaque material. Visualization of dosage form by X-ray is due to the inclusion of a radio-opaque material. The formulation is administered by natural swallowing followed by 50 mL of water. The radiographic imaging is taken from each animal in a standing position, and the distance between the source of X-rays and the animal should kept constant for all imaging, so that the tablet movement could be easily noticed. Gastric radiography was done at 30-min time intervals for a period of 5 h using an X-ray machine. Gamma scintigraphy is a technique whereby the transit of a dosage form through its intended site of delivery can be non-invasively imaged in vivo via the judicious introduction of an appropriate short lived gamma emitting radioisotope. The inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner. But the main drawback of γ- scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceutical.

11) Pharmacokinetic studies
Pharmacokinetic studies include AUC (Area under Curve), Cmax, and time to reach maximum plasma concentration (Tmax) were estimated using a computer. Statistical analyses were performed using a Student t test with p, 0.05 as the minimal level of significance.

12) Specific Gravity
Displacement method is used to determine the specific gravity of floating system using benzene as a displacing medium.

APPLICATION OF FDDS
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 follows.
1. Sustained Drug Delivery
HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

2. Site-Specific Drug Delivery
These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.

3. Absorption Enhancement
Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. E.g. 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>
<thead>
<tr>
<th>Sr. No</th>
<th>Dosage Forms</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Floating tablet</td>
<td>Acetaaminophen, Acetylsalicylic acid, Ampicillin, Ampicillin trihydrate, Atenolol, Captopril, Cinnerzine, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbide mononitrate, p-aminobenzoic acid</td>
</tr>
<tr>
<td>2</td>
<td>Floating capsule</td>
<td>Furosemide, L-DOPA, Benserazide, Nicardipine, Misoprostol, Propanolol, Pepstatin</td>
</tr>
<tr>
<td>3</td>
<td>Floating microsphere</td>
<td>Aspirin, Grisofulvin, p-nitro aniline, Ibuprofen, Terfinadine, Tranilast</td>
</tr>
<tr>
<td>4</td>
<td>Floating granules</td>
<td>Cinnerzine, p-aminobenzoic acid, prednisolon, quinidine gluconate.</td>
</tr>
<tr>
<td>5</td>
<td>Powders</td>
<td>Several basic drugs- Riboflavin phosphate, Sotalol, Theophylline</td>
</tr>
<tr>
<td>6</td>
<td>Film</td>
<td>Cinnerzine, p-aminobenzoic acid, prednisolon, quinidine gluconate</td>
</tr>
<tr>
<td>7</td>
<td>Multiple unit floating dosage form</td>
<td>Clarithromycin, p-aminobenzoic acid</td>
</tr>
<tr>
<td>8</td>
<td>Bilayer Tablet</td>
<td>Misoprostal</td>
</tr>
<tr>
<td>9</td>
<td>Foams/ Hollow Bodies</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>10</td>
<td>Floating controlled release capsule</td>
<td>Levodopa, Benserazide</td>
</tr>
<tr>
<td>11</td>
<td>Effervescent floating liquid preparation</td>
<td>Aluminium hydroxide, Magnesium carbonate</td>
</tr>
<tr>
<td>12</td>
<td>Floating liquid alginate preparation</td>
<td>Aluminium-Magnesium antacid</td>
</tr>
<tr>
<td>13</td>
<td>Colloidal gel forming FDDS</td>
<td>Ferrous sulphate</td>
</tr>
</tbody>
</table>

Fig 3: Dosage Forms of FDDS with Examples of Various Drugs
FUTURE POTENTIAL
FDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) which are absorbed from very specific regions of GI tract and whose development has been halted due to the lack of appropriate pharmaceutical technologies. In addition, by continual supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoetin, vasopressin, insulin, low molecular weight heparin, and LHRH. Some of the unresolved critical issues related to the rational development of FDDS include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics. However, we are as close as we have ever been to see a greater transition of gastric retention devices from developmental level to the manufacturing and commercial level.

REFERENCES