A REVIEW ON FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of this review on floating drug delivery systems (FDDS) is to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the gastro intestinal tract is to control the gastric residence time, using gastroretentive dosage forms that will provide us with new and important therapeutic options. From the formulation technological point of view, the floating drug delivery system is considerably easy and better approach. The development of FDDS are including physiological and formulation variables affecting gastric retention, approaches to design single unit and multiple unit floating systems, advantages, formulation variables and their classifications are covered in detail. This review also summarizes the in vitro techniques, the in vivo studies to evaluate the performance and application of floating systems. These systems are useful to several problems encountered during the development of pharmaceutical dosage form. An attempt has been made in this review article to introduce the readers to the current technological developments in floating drug delivery.

Keywords: Floating drug delivery system, Classification, Evaluation, Buoyancy.

INTRODUCTION

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. 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.[1]
The high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms. Although tremendous advances have been seen in oral controlled drug delivery system in the last two decades, this system has been of limited success in the case of drugs with a poor absorption window throughout the GIT (gastrointestinal tract). In the development of oral controlled drug delivery system, one of the main challenges is to modify the GI transit time. Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence times usually range between 5 min and 2 h. In the fasted state the electrical activity in the stomach, the inter-digestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and hence the transit of dosage forms. It is characterized by four phases: Phase I–period of no contraction (40–60 min), phase II–period of intermittent contractions (20–40 min), phase III–period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave (10–20 min), and phase IV–period of transition between phase III and phase I (0–5 min).\(^2\)

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 exists today.\(^3\) Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS)\(^4\), low-density systems\(^5\), raft systems incorporating alginate gels\(^6\), bioadhesive or mucoadhesive systems\(^7\), high-density systems\(^8\), superporous hydrogels\(^9\) and magnetic systems.\(^10\)

Gastro-retention is essential for drugs that are absorbed from the stomach, drugs that are poorly soluble or degraded by the higher pH of intestine, and drugs with an absorption which can be modified by changes in gastric emptying time. Gastro-retentive dosage forms are also useful for local as well as sustained drug delivery for certain conditions, like \textit{H. pylori} infection which is the cause of peptic ulcers. This dosage form improves bioavailability, therapeutic efficacy and may even also allow a possible reduction in the dose because of steady therapeutic levels of drug, for example: furosemide and ofloxacin. The reduction in fluctuations in therapeutic levels minimizes the risk of resistance especially in case of \textit{\beta}-lactam antibiotics (penicillins and cephalosporins).\(^11\)

Controlled gastric retention of solid dosage form may be achieved by the mechanism of mucoadhesion, floatation, sedimentation, expansion, modified shape system or by
simultaneous administration of pharmacological agents which delay gastric emptying. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to 2 complications

- Short gastric residence time.
- Unpredictable gastric emptying rate.\textsuperscript{[12]}

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are 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.\textsuperscript{[13]}

**Floating drug Delivery System**

Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at 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. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. 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.\textsuperscript{[14]}

Floating dosage form with prolonged residence time in stomach is highly desirable for drug

- That are locally active in stomach
- That have absorption window in stomach or in upper small intestine.
• That is unstable in intestinal or colonic environment.
• Have low solubility at high pH value.\textsuperscript{[15]}

**Drug Candidates Suitable for floating Drug Delivery**
1. Drugs which shows site-specific absorption in the stomach or upper parts of the small intestine. For example: furosemide, riboflavine-5-phosphate.
2. The drugs which are unstable in the lower part of GIT. For example: captopril
3. Drugs required to exert local therapeutic action in the stomach. For example: antacids, anti-\textsuperscript{-}H.pylori agents, misoprostol
4. Drugs with variable bioavailability. For example: satolol HCl.
5. Drugs which are insoluble in intestinal fluids. For example: quinidine, diazepam. \textsuperscript{[16]}

**MECHANISM OF FLOATING SYSTEMS**
Floating drug delivery systems (FDDS) have bulk density lesser than gastric fluid, so they remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug released slowly at the desired rate from the system as shown in Fig 1. 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 function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side as shown in Fig 1. This apparatus helps in optimizing FDDS with respect to stability and durability of floating force produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations. \textsuperscript{[17]}

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

Where, \( F = \) total vertical force; \( D_f = \) fluid density; \( D_s = \) object density;
\( v = \) volume and \( g = \) acceleration due to gravity
Fig. 1. Mechanism of floating systems

TYPES OF FLOATING DRUG DELIVERY SYSTEMS

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

i) Non-Effervescent FDDS [18,19]

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.

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. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

b. Bi-layer Floating Tablets: A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.
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. 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 °C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The micro-balloons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.

ii) Effervescent FDDS

a. Volatile liquid containing system: The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.[23]

b. Gas-generating Systems: These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO₂, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.[20,21] The carbon dioxide generating components may be intimately mixed within the tablet matrix to produce a single-layered tablet or a bi-layered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for the prolonged release effect.[22]
ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM

1. The Gastroretentive systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.

2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.

3. 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. \(^{23,24}\)

4. The gastro retentive systems are advantageous for drugs meant for local action in the stomach. E.g. antacids.

5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

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11. FDDS improves patient compliance by decreasing dosing frequency.
12. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.
13. Better therapeutic effect of short half-life drugs can be achieved.
14. Gastric retention time is increased because of buoyancy.
15. Enhanced absorption of drugs which solubilise only in stomach.
16. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
17. Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.[25]

DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM
1. Floating system is not feasible for those drugs that have solubility or stability problem in GIT.
2. The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.[26]
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
5. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
6. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
7. Some drugs present in the floating system causes irritation to gastric mucosa.

EVALUATION OF FLOATING DOSAGE FORM
A. For Single Unit Dosage Forms (ex: tablets)
i. Floating lag time: It is the time taken by the tablet to emerge onto the surface of dissolution medium and is expressed in seconds or minutes.
ii. In vitro drug release and duration of floating: This is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37 ± 0.2 °C in Simulated gastric
fluid (pH 1.2 without pepsin). Aliquots of the samples are collected and analyzed for the
drug content. The time (hrs) for which the tablets remain buoyant on the surface of the
dissolution medium is the duration of floating and is visually observed.

iii. *In vivo* evaluation for gastro-retention: This is carried out by means of X-ray or  
Gamma scintigraphic monitoring of the dosage form transition in the GIT. The tablets are also 
evaluated for hardness, weight variation, etc.

**B. For Multiple Unit Dosage Forms (ex: floating beads)**

Apart from the *In vitro* release, duration of floating and *in vivo* gastro-retention tests, the 
multiple unit dosage forms are also evaluated for

i. Morphological and dimensional analysis with the aid of scanning electron microscopy 
(SEM). The size can also be measured using an optical microscope.

ii. % yield of beads: This is calculated from Weight of beads obtained x 100 Total weight of 
drug and polymer.

iii. Entrapment efficiency: The drug is extracted by a suitable method, analyzed and is calculated 
from Practical amount of drug present ×100 Theoretical drug content.

iv.a) *In vitro* floating ability (Buoyancy %): A known quantity of microspheres are spread 
over the surface of a USP (Type II) dissolution apparatus filled with 900 ml of 0.1 N HCl 
containing 0.002% v/v Tween 80 and agitated at 100 rpm for 12 hours. After 12 hours, the 
floating and settled layers are separated, dried in a dessicator and weighed. The buoyancy is 
calculated from the following formula. Buoyancy (%) = Wf / ( Wf + Ws) * 100 Where Wf 
and Ws are the weights of floating and settled microspheres respectively.
b) Floating Test: 
The in vitro buoyancy was determined by floating lag time. Here, the tablets were placed in 
a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface 
and float was determined as floating lag time and total duration of time by which dosage 
form remain buoyant is called Total Floating Time (TFT).[27]

v. Drug-excipient (DE) interactions: This is done using FTIR. Appearance of a new peak, 
and/or disappearance of original drug or excipient peak indicates 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.
FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The Gastric Retention Time (GRT) of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex, sleep and disease state of the individual (e.g., gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agent (cisapride and metoclopramide).

1. Density of dosage form
Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention. A density of less than 1.0 gm/cm$^3$ is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium.[28]

2. Size of dosage form
The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form the greater will be the gastric retention time[29] because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. The size of the dosage form appears to be an important factor affecting gastric retention.

3. Food intake and nature of food
Food intakes, the nature of the food, caloric content, and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the stomach influences the GRT of the dosage form. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption site for a longer time. Gamma scintigraphic study of a bilayer floating capsule of misoprostol; the mean gastric residence time was 199±69 minutes; after a light breakfast, a remarkable enhancement of average GRT to 618±208 minutes was observed. The above results are supported by the experiments of whitehead et al [30] which show an increase in the relative heights of the floating units after meal consumption.
4. Effect of gender, posture and age
A study found that females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men. The authors also studied the effect of posture on GRT, and found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. On the other hand, in a comparative study in humans have been studied.[31] The floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of similar size.

5. Caloric content
GRT can be increased with meal that is higher in protein and fat.

List of Commercial floating formulations

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Delivery system</th>
<th>Drug(dose)</th>
<th>Company name</th>
</tr>
</thead>
<tbody>
<tr>
<td>MadoparHBS®</td>
<td>Floating,Crcapsule</td>
<td>Benserazide (25mg)</td>
<td>Roche products,USA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L-Dopa (100mg)</td>
<td></td>
</tr>
<tr>
<td>Valrelease®</td>
<td>Floating capsule</td>
<td>Diazepam (15mg)</td>
<td>HoffmannLaroche,USA</td>
</tr>
<tr>
<td>Liquid Gaviscon®</td>
<td>Effervescent floating liquid alginate preparations</td>
<td>Al hydroxide(95mg) Mg Carbonate(358mg)</td>
<td>Glaxosmithkline,India</td>
</tr>
<tr>
<td>Topalkan®</td>
<td>Floating liquid alginate preparation</td>
<td>Al-mg antacid</td>
<td>Pierre Fabre drug,France</td>
</tr>
<tr>
<td>Almagate float coat®</td>
<td>Floating dosage form</td>
<td>Al-Mg antacid</td>
<td>-------</td>
</tr>
<tr>
<td>Conviron®</td>
<td>Colloidal gel forming FDDS</td>
<td>Ferrous sulphat</td>
<td>Ranbaxy,india</td>
</tr>
</tbody>
</table>
Cytotech® Bilayer floating capsule Misoprostol(100µg/200µg) Pharmacia,USA
Cifran OD® Gas-generating floating form Ciprofloxacin(1gm) Ranbaxy,india

APPLICATIONS
Floating drug delivery system offers several applications for drugs having poor bioavailability because of narrow absorption window in the upper part of GIT. It retains the dosage forms at the site of absorption and thus enhances the bioavailability. They are mainly applied in the following:

- Sustained drug delivery
- Site specific drug delivery
- Absorption enhancement\(^{[32]}\)

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

CONCLUSION
Controlled release floating drug delivery system is a promising delivery system, to provide a potential approach for gastric retention. Developing an efficient FDDS is a real challenge and the drug delivery system must remain for sufficient time in stomach. Various approaches have been employed to develop FDDS has emerged as one of the most promising gastro-retentive drug delivery system. The FDDS has an additional advantage for drugs
that are absorbed primarily in the upper part of the GIT, i.e., the stomach, duodenum, and jejunum. 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 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.

REFERENCES