

## Review Article

### A REVIEW ON FLOATING DRUG DELIVERY SYSTEMS

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#### ABSTRACT

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. This results in a significant fluctuation in drug levels. Recently, several technical advancements had introduced. The idea of gastric retention comes from the need to localize drugs at a specific region of gastrointestinal tract (GIT) such as stomach in the body. Many drugs get absorbed only in the upper intestinal tract, designing such molecules as once-daily formulations are exclusive for these molecules. Thus GI retention platforms had emerged. One of the major challenges in developing gastric retention device is overcoming the house keeping waves particularly in the fasted state. Often, the extent of drug absorption is limited by the gastric residence time (GRT) of the drug at the absorption site. If the drugs are poorly soluble in intestine due to alkaline pH, gastric retention may increase solubility before they are emptied, resulting in improved gastrointestinal absorption of drugs with narrow absorption window as well as for controlling release of drugs having site-specific absorption limitation. Gastroretention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastroretention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients.

#### KEY WORDS

Fasted state, gastric residence time, gastroretention, gastrointestinal tract, narrow absorption window.

#### INTRODUCTION

Floating drug delivery systems (FDDS) are aimed to retain the drug in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. The underlying principle is very simple i.e., to make the dosage form less dense than the gastric fluids so that it can float on them. The density of the system can be reduced by incorporating a number of low density fillers into the

systems such as hydroxyl cellulose, lactates or microcrystalline cellulose. However, this system is not ideal because its performance is highly dependent on the presence of food and fluid in the stomach. The basic idea behind the development of such a system was to maintain a constant level of drug in the blood plasma inspired by the fact that the drug dose does not undergo disintegration. The drug usually keeps floating in the

gastric fluid and slowly dissolves at a pre-determined rate to release the drug from the dosage form and maintain constant drug levels in the blood<sup>1</sup>.

The concept of floating tablets is mainly based on the matrix type drug delivery system such that the drug remains embedded in the matrix which after coming in contact with the gastric fluid swells up and the slow erosion of the drug without disintegration of the tablet takes place. Sometimes for generating a floating system we even need to add some effervescent or gas generating agent which will also ultimately reduce the density of the system and serve the goal of achieving a floating system. These systems have a particular advantage that they can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT. These systems continuously release the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Different approaches are currently used to prolong the gastric retention time, like hydro dynamically balanced systems, swelling and expanding systems, polymeric bio-adhesive systems, modified shape systems, high density systems and other delayed gastric

emptying devices. 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<sup>2</sup>.

Based on the mechanism of buoyancy two distinctly different technologies

1. Non-effervescent system
2. Effervescent system

### **Non-effervescent system**

In this system commonly used excipients are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel forming hydrocolloid which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air entrapped by the swollen polymer confers buoyancy to these dosage forms. The gel structure acts as a reservoir for sustained drug release since the drug is slowly released for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier<sup>3</sup>.

### **Effervescent system**

These floating systems are prepared with swellable polymers such as methocel or polysaccharides like chitosan and effervescent component containing sodium bicarbonate, citric and/or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the gelyfied hydrocolloid.

This produces an upward motion of the dosage form and maintains its buoyancy. 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<sup>4</sup>.

### **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. FDDS have a bulk density less than gastric fluids and so remain buoyant in the

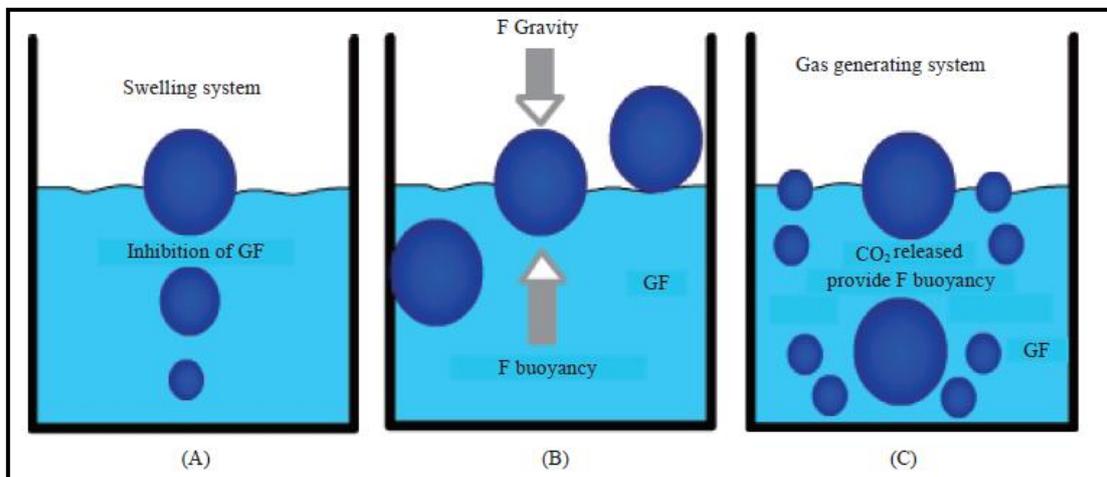
stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration<sup>5</sup>.

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<sup>6</sup>.

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<sup>7</sup>.

$$F = F_{\text{buoyancy}} - F_{\text{gravity}} = (D_f - D_s) gv$$

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

This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra-gastric buoyancy capability variations.

#### **Advantages of FDDS**

FDDS is highly advantageous in the treatment of the disorders related to the stomach. As the prime objective of such systems is to produce a gastro retentive product or a product which has an enhanced retention time in the stomach<sup>8</sup>.

➤ Drugs with considerably short half life can be administered in this manner to get an appreciable therapeutic activity.

- Enhancement of the bioavailability for drugs which can be metabolized in the upper GIT.
- They also have an advantage over the conventional system as it can be used to overcome the adversities of gastric retention time as well as the gastric emptying time.
- The duration of treatment through a single dose, which releases the active ingredient over an extended period of time
- The active entity is delivered specifically to the site of action, thus minimizing or eliminating the side effects.

**Disadvantages of FDDS:**

- 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<sup>9</sup>
- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
- High variability in gastric emptying time due to its all (or) non-emptying process.
- Patients should not be dosed with floating forms just before going to bed.
- Floating system is not feasible for those drugs that have solubility (or) stability problem in gastric fluids.
- The dosage form should be administered with a minimum of glass full of water (200-250 ml).

- The drugs, which are absorbed throughout GIT, which under go first-pass metabolism (Nifedipine, Propranolol etc.), are not desirable candidate.

**Suitable drug candidates for FDDS**

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. In general, appropriate candidates for FDDS are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT<sup>10-14</sup>.

- Drugs with narrow absorption window in GIT, e.g., Riboflavin and Levodopa
- Drugs that primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, chlordiazepoxide and cinnarazine.
- Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
- Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., Amoxicillin Trihydrate

## **METHODS FOR PREPARING FLOATING DOSAGE FORM**

Following approaches can be used for preparing floating dosage forms<sup>15-17</sup>:

- ❖ Using gel-forming hydrocolloids such as hydrophilic gums, gelatin, alginates, cellulose derivatives, etc.
- ❖ Using low-density enteric materials such as methacrylic polymer, cellulose acetate phthalate.
- ❖ By reducing particle size and filling it in a capsule.
- ❖ By forming carbon dioxide gas and subsequent entrapment of it in the gel network.
- ❖ By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.
- ❖ By incorporation of inflatable chamber, which contained in a liquid e.g. solvent that gasifies at body temperature to cause the chambers to inflate in the stomach

## **FACTORS AFFECTING THE FDDS**

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system<sup>18-21</sup>:

- **Density:** Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.
- **Size:** Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
- **Shape of dosage form:** Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 h compared with other shapes.
- **Single (or) multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles (or) containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

- **Fed or unfed state:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity (or) the Migrating Myoelectric Complex (MMC) that occurs every 1.5 to 2 h. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- **Nature of meal:** Feeding of indigestible polymers (or) fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- **Caloric content:** GRT can be increased by four to 10 h with a meal that is high in proteins and fats.
- **Frequency of feed:** The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender:** Mean ambulatory GRT in males ( $3.4 \pm 0.6$  h) is less compared with their age and race matched female counterparts ( $4.6 \pm 1.2$  h), regardless of the weight, height and body surface).
- **Age:** Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration:** Anti-cholinergics like Atropine and Propantheline, opiates like Codeine and prokinetic agents like Metoclopramide and Cisapride; can affect floating time.

#### **PHARMACOKINETIC AND PHARMACODYNAMIC ASPECTS OF FDDS**

- The aim of this section is to delineate these aspects in order to suggest rational selection of drugs for which FDDS would be a beneficial strategy<sup>22-25</sup>

#### **Pharmacokinetic aspects**

- **Absorption window:** Validation that the drug is within the category of

narrow absorption window agents currently various experimental techniques are available that permit us to verify the absorption properties of the tested molecule, to determine the mechanism of intestinal absorption and to elucidate the permeability at different regions of the GI tract. In the case of absorption by active transporters that are capacity limited, the efficacy of the transport activity may increase following sustained presentation of the drug to the transporting enzymes in comparison to non-control release mode of administration.

➤ **Enhanced bioavailability:**

Once it has been ascertained that the compound in question is defined as narrow absorption window, the possibility of improving bioavailability by continuous administration of the compound to the specific site should be tested. For example, we have found that certain bisphosphonates, including alendronate, are absorbed directly from the stomach. However, the magnitude of this pathway remains modest even in the case where the prolonged gastric retention of the bisphosphonate in rats is produced by

experimental/surgical means. On the other hand, the bioavailability of control release (CR) floating systems of Riboflavin and Levodopa are significantly enhanced in comparison to administration of simple CR polymeric formulations. It may be concluded that several different processes, related to absorption and transit of the drug in the gastrointestinal tract, act concomitantly and influence the magnitude of drug absorption. Therefore, *in vivo* studies are necessary to determine the release profile of the drug from the dosage form that will provide enhanced bioavailability<sup>26</sup>.

➤ **Enhanced first pass biotransformation:**

In a similar fashion to increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

➤ **Improved bioavailability due to reduced P-glycoprotein (P-gp) activity in the duodenum:**

In apparent contrast to the higher density of CYP3A4 at the upper part of the intestine, P-gp mRNA levels increase longitudinally along the intestine such that the highest levels are located in the colon. Therefore, for drugs that are P-gp substrate and do not undergo oxidative metabolism, such as Digoxin, floating systems may elevate absorption compared to the immediate and CR dosage forms.

➤ **Reduced frequency of dosing:** For drugs with relatively short biological half-life, sustained and slow input from control release floating system may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

➤ **Targeted therapy for local ailments in the upper GIT:** The prolonged and sustained administration of the drug from the floating systems to the stomach may be advantageous for local therapy in the stomach and the small intestine.

**PHARMACODYNAMIC ASPECTS OF FDDS:**

**Reduced fluctuations of drug concentration:** Continuous input of the drug following floating system administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects 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.

**Improved selectivity in receptor activation:** Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

**Reduced counter-activity of the body:** In many cases, the pharmacological response, which intervenes with the natural physiologic processes, provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

**Minimized adverse activity at the colon:** Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for floating formulation for beta-lactam antibiotics that are absorbed only from the small intestine and presence in the colon leads to development of microorganisms<sup>27</sup>.

#### **Evaluation of Floating Tablets**

The formulated tablets were evaluated for common physical evaluation tests like weight variation, thickness, hardness, drug content and in-vitro dissolution test apart from this the floating tablets also evaluated for floating time, floating lag time and in vivo – invitro tests as per following procedures.

**Buoyancy / Floating Test:** The in vitro buoyancy was determined by floating lag time, as per the method described by a Rosa et al., 1994. 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)<sup>28</sup>.

**In-vitro dissolution study:** The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 1h, 2h, 3h, 4h, 5h, 6h, 8h, 10 h and 12h. The volume of dissolution fluid adjusted to 900 ml by replacing fresh 5ml of dissolution medium after each sampling. The release studies were conducted with 3 tablets, and the mean values were plotted versus time. Each sample was analyzed at maximum wavelength using double beam UV visible spectrophotometer against reagent blank.

**In vivo confirmation of buoyancy by using radiographic studies:** For this study the tablets were prepared by replacing half of the amount of drug with barium sulfate. After overnight fasting of three healthy volunteers they were fed with low calorie food and allowed to take water after these tablets were administered orally. Radiographs were obtained at specific time intervals, over these periods volunteers were allowed to take water<sup>29</sup>.

#### **Application of floating drug delivery systems**

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<sup>30</sup>

**1. Sustained drug delivery:** FDDS 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.

E.g. Sustained release floating capsules of Nicardipine Hydrochloride

**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

**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%)

S.No	Product	Active Ingredients
1	Madopar	Levodopa and benserzide
2	Valrelease	Diazepam
3	Topalkan	Aluminum magnesium Antacid
4	Almagate	flatcoat Antacid
5	Liquid gavi-son	Alginic acid and sodium bicarbonate

**Table 1: Marketed products of FDDS** <sup>31</sup>

**CONCLUSION**

Developing an efficient FDDS is a real challenge and the drug delivery system

must remain for a sufficient time in the stomach. Various techniques and 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.

#### **FUTURE POTENTIAL**

Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying. Buoyant delivery system considered as

a beneficial strategy for the treatment of gastric and duodenal cancers. The floating concept can also be utilized in the development of various anti-reflux formulations and these are potential to treat the Parkinson's disease.

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