Floating Drug Delivery System: A versatile Platform for Gastric Retention

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ABSTRACT

Though the oral controlled drug delivery systems (DDS) offer a very attractive strategy for drug delivery, their efficiency is complicated by a number of physiological adversities. These include impulsive gastric emptying times (GET) and little gastric residence time (GRT). These, in turn, present a significant problem in complete release and absorption for drugs having narrow absorption window. Thus, there exists a challenge until all the drug is completely released for sustain drug release well as to extend the presence of dosage form in stomach or upper part of small intestine. A number of approaches have proved to be useful in prolonging the GRT of the controlled oral delivery systems. Prominent among them is the floating drug delivery systems (FDDS). This article gives a comprehensive review of the FDDS approach that has now become a leading methodology in the field of oral controlled and site specific drug delivery. Including patented and clinically available products, their formulation development strategies, classification, advantages and limitations in Current technological developments in FDDS are discussed.

KEYWORDS: Gastric residence time; hydrodynamically balanced systems; Modified-shaped systems; Floating drug delivery system, Oral route
1. INTRODUCTION

For systemic action Oral route of drug delivery is commonly employed route due to patient compliance, ease of administration and flexibility in formulation has been the most versatile, expedient. Oral route of administration for controlled release (CR) systems, is the first choice because as compared to any other route gastrointestinal physiology allows us to design more varied dosage forms. In achieving a plethora of controlled release objectives oral dosage forms have proved to be successful ranging from immediate release to site specific delivery. Although oral formulations still control more than 60% of the market over other routes used. Different types of oral formulations such as delayed release, fast dissolving, taste masking formulations and controlled release are being developed [1].

Oral controlled release DDS facilitates the oral delivery of drugs at predictable and reproducible rates throughout the course of their GI transit. The major goal of oral controlled DDS is to achieve more predictable and better bioavailability of drugs. However, their success is limited by several physiological problems [3] such as:

1) Fluctuations in the gastric emptying process
2) Narrow absorption window
3) Stability problems in the intestine
4) Within the desired regions of the GIT Inability to restrain and localize the DDS.

In non-diseased state, depending upon the physiological state of the subject and the design of pharmaceutical formulation the gastric emptying time of a dosage form varies from a few minutes to even 12 h. Since, most of drugs are preferentially absorbed in the upper part of the small intestine, this variation may lead to unpredictable bioavailability [4].

In humans, the relatively short gastric emptying time, which normally averages 2-3 hrs through the major absorption zone (stomach or upper part of the intestine), leads to decreased efficacy of the administered dose and can result in incomplete drug release from the DDS. Thus, placement of a DDS especially for drugs exhibiting narrow absorption window, stability problems in the intestine, main absorption from the stomach, pH, local activity in the stomach, poor solubility at basic and property to undergo degradation in the colon in a
specific region of the GIT offers numerous advantages. Generally with the absorbing membrane the intimate contact of the DDS has the potential to maximize drug absorption and also control the rate of drug absorption. To the development of oral CR dosage forms with longer gastric retention capabilities. All these considerations have led [5].

2. BASIC FUNCTIONING OF GIT

2.1 Anatomy and Physiology of stomach

Based on anatomy and physiology of GIT, the design and evaluation of FDDS is decided. Situated in the left upper part of the abdominal cavity immediately under the diaphragm the stomach is a J-shaped dilated portion of the alimentary tract. According to the amount of distension its size varies i.e. from 25-50 ml in collapsed state to 1500 ml following a meal. The stomach is further separated into three parts i.e. fundus, body, and antrum (Fig 1).

The pylorus is an anatomical sphincter between the most terminal antrum and the duodenum. The fundus and the body store food momentarily, secrete digestive juices and impel chyme, to the antrum. The antrum grinds and triturates food particles and regulates the secretion of hydrochloric acid and empties the food [6].

2.2 Factors Affecting Gastric Retention

2.2.1 Physiological factors

There are a number of factors that influence gastric emptying of an oral dosage form. These factors include size, and shape of dosage form, concomitant intake of food, drugs, density, and biological factors such as posture, age, gender, body mass index and disease states (e.g., diabetes, Crohn’s disease. Additionally, physical exercise may also affect gastric emptying. Stress is also known to enhance while depression is known to reduce the gastric emptying rate [7].

Presence of food also affects the GRT of floating as well as non-floating dosage forms. According to a report by Muller-Lissner et al. (1981) after a fat and protein test meal a GRT of 4 to 10 h could be achieved. By the nature, caloric content and the frequency of intake of food the GRT of dosage form is affected. For example, after a single light meal (breakfast) the mean GRT of a bilayer floating capsule of misoprostol was reported to be 3.3 ± 1.15 min. However, after a string of meals, the GRT was found to increase to 10.3 ± 3.5 min. Even the
gender, posture and age have been reported to alter the gastric retention of indigestible solid [8].

The gastric residence period of a dosage form depending on the subject posture (either standing or supine), has been reported to be a function of either its buoyancy or the diametric size of the matrix. A triple radionuclide scintigraphic technique has been reported for intragastric monitoring to measure the effects of formulation parameters (diameter, flexibility and density of matrices) with the physiological parameters such as subject posture on GRT [9].

2.2.2 Dosage form factors

On the floating behaviour density of the dosage form has a very intense effect. In general, the than the gastric contents density of the dosage form should be less. In the literature a density of less than 1.0g/ml has been reported. However, the bulk density of dosage is not the only factor for unfolding its buoyant capabilities because the later by resultant-weight measurements and swelling experiments are better monitored and –represented. Other factors that also affect the GRT include adhesion of FDDS to the gastric mucosa [10].

3. TECHNOLOGICAL DEVELOPMENTS IN FDDS

Basically, the systems having a bulk density less than gastric fluids are floating drug delivery systems. For a prolonged period of time they remain buoyant in the stomach and defy the gastric emptying rate. At the desired rate from the system the floating of system on the gastric contents allows the drug to be released slowly.

The different buoyant formulations include hollow microspheres (microballoons), granules, powders, capsules, tablets (pills), and laminated films [11]. A list of some drugs for which FDDS have been developed is given in Table 1.

4. TYPES OF FDDS

FDDSs have been classified into two distinctly different technologies, i.e. non-effervescent and effervescent systems on the basis of their mechanism of buoyancy [12]. The various approaches used in their formulation are:

4.1. Non-effervescent FDDS
These are the buoyant systems, which when given orally, swell in the presence of gastric fluid in a manner that allows the maintenance of relative integrity of shape and a bulk density of less than 1g/ml. Swelling of the system may take place due to the presence of gel forming swellable type hydrocolloids, polysaccharides and matrix forming polymers, like polymethacrylates, polycarbonates, polystyrenes, polyacrylates and bioadhesive polymers like chitosan and carbopol. This swollen system also acts as a gelatinous barrier through which the drug is released by diffusion at a controlled rate [13].

The non effervescent FDDS can be further subdivided into four types:

(i) Colloidal gel barrier system

This hydrodynamically balanced system incorporates a drug in one or more gel-forming swellable type hydrocolloids. It remains buoyant in the stomach, thereby, extending the gastric retention time. This allows the maximum amount of drug to reach its absorption sites in the solution form [14]. Most commonly used excipients include hydroxypropyl cellulose, hydroxyethylcellulose, hydroxypropyl methyl cellulose (HPMC), matrix-forming polymer i.e. polycarbophil, polyacrylate and polystyrene and polysaccharides. Some polymers which are used in preparation of GRDDS are given in table 2.

(ii) Microporous compartment system

Within a microporous compartment having pores in its top and bottom walls it involves encapsulation of a drug reservoir. With entrapped air that allows it to float over the gastric contents the device has a floatation chamber. The peripheral walls are completely sealed to prevent any physical contact of the undissolved drug with gastric surface. The gastric fluid enters the device through the pores, dissolves the drug and carries it for absorption [15].

(iii) Multiparticulate Floating Drug Delivery System

To formulate multiple unit floating dosage forms freeze dried calcium alginate has been used. By addition of sodium alginate solution drop wise to aqueous solution of CaCl₂ resulting in precipitation of calcium alginate spherical beads with diameter of approximately 2.5 mm are prepared and then separated and snap-frozen in liquid nitrogen. These are then lyophilized at -40 °C for 24 h leading to formation of porous system having floating ability of more than 12 h. These floating beads exhibit an extended gastric residence time of more than 5.5 hours [16].
(iv) Hollow microspheres / Microballoons

By the novel emulsion solvent diffusion method hollow microspheres loaded with ibuprofen in their outer polymeric shell were prepared. For this, ethanol/ dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of polyvinyl acetate maintained at 40 °C. Dichloromethane evaporated leading to formation of microspheres which floated continuously over the surface of a surfactant containing acidic dissolution media for more than 12 h [17].

(v) Bioadhesive Floating Systems

Between a bioadhesive system and a floating system a synergism has also been explored [18]. A series of bioadhesive cross-linked forms of polymers of methacrylic acid (PMA) and acrylic acid (PAA) were prepared. Isosorbide mononitrate floating tablets were prepared and then coated (by dip method) either with Carbopol® suspensions or 0.5% suspension of these bioadhesive polymers in 0.5% Carbopol® gel, and then air-dried. To show better adhesive properties at pH 1.0 as compared to those coated with Carbopol® the tablets coated with bioadhesive polymers were found. The coated tablets also showed lower densities indicating that the polymer coat might confer buoyancy to these tablets [19].

(vi) Miscellaneous

A strategy used for the triple drug treatment of Helicobacter pylori associated peptic ulcer involved the preparation of a triple layer floating tablet [20]. As rate controlling polymers the three drugs i.e. tetracycline, metronidazole and bismuth salt were used with HPMC and poly(ethylene oxide). In the core layer of the triple-layer matrix for controlled delivery Tetracycline and metronidazole were included, while bismuth salt was included in one of the external layers for instant release and results showed a sustained delivery of tetracycline and metronidazole over 6-8 h [21]. The drug release was found to be affected by alterations in the ratio of matrix-forming polymers and the foam powder. The structure of this low density floating matrix tablet is shown in Fig 2.

4.2. Effervescent FDDS

These are the buoyant delivery systems which utilize matrices prepared with swellable polymers (such as Methocel®), polysaccharides (e.g., chitosan, sodium alginate) and effervescent (gas generating) components (like sodium bicarbonate with citric or tartaric...
acid) or matrices containing chambers of liquid that gasifies at body temperature [22]. The matrices are designed in such a way that upon entrance in the stomach, carbon dioxide is liberated due to action of the gastric juice and is trapped in the gelified hydrocolloid. This makes the dosage form to move upward and maintain its buoyancy.

A multiple-unit type of floating pill comprising of two layers, which generates CO₂ gas, was developed [23]. On diffusion of water through the outer swellable membrane layers, carbon dioxide was generated leading to the decrease in density (Fig. 3).

5. DEVELOPMENT AND EVALUATION OF FDDS

5.1. Prerequisites

The development of an optimum CR dosage form is based on understanding of the basic principles of GI dynamics such as gastric emptying, small intestinal transit, colonic transit etc. [24]. Knowledge about the bioavailability of drug from different parts of GIT, and factors that can alter or limit the drug absorption further assist in designing the type of dosage form that is needed for a particular drug. Thus, for the formulation of a HBS, the dosage form should satisfy three major conditions i.e. it must have sufficient structure to form a cohesive gel barrier, it should maintain an overall bulk density lower than that of gastric fluid and it should serve as a reservoir for delivery system from where the drug is released slowly at a controlled rate [25].

5.2. Evaluation of FDDS

Evaluation of a drug product is done to evaluate the performance characteristics and batch-to-batch quality control. Apart from the routine tests like general appearance, hardness and friability, drug content, weight variation, uniformity of content, dissolution time, drug release etc., the FDDS need to be evaluated for gastroretentive performance by carrying out in vitro and in vivo tests [26].

5.2.1. In vitro evaluation

1. Buoyancy lag time (Floating lag time): It is the time taken by the floating dosage form to emerge on the surface of release medium which can be either 0.1 N HCl (Jaimini et al., 2007) or artificial gastric fluid [27].
2. Buoyancy time (Total floating time): It is the duration of time during which the dosage form floats on the surface of the medium which is usually simulated gastric or intestinal fluid maintained at 37°C. The floating time is determined by using the USP Dissolution apparatus containing 900 ml of 0.1 N HCl maintained at 37°C [27].

3. Specific Gravity: It can be determined by the displacement method using benzene as a displacing medium [27].

4. Floating Forces (Resultant-Weight): It is not possible to evaluate the floating force from a single density determination made before immersion of the dosage form. Since the dry material of which it is made, progressively reacts or interacts within the fluid to release its drug contents, an in vitro measuring apparatus was designed to evaluate the actual floating capabilities of the buoyant dosage forms as a function of time [28].

5. Size Measurement: To evaluate the influence of buoyancy on gastric residence time of dosage forms, factors such as shape, initial size and leveling kinetics of the dosage forms must be estimated. Non-disintegrating dosage forms from 3-7 mm in diameter can be expelled from the human stomach during the postprandial period [28].

5.2.2. In vivo Evaluation

The in vivo gastric retention potential of floating dosage form is generally evaluated by γ-scintigraphy or roentgenography. For this, studies are done both under fasted and fed conditions using floating and non-floating (control) dosage forms. However, care needs to be taken that both dosage forms are non-disintegrating and that the subjects are young and healthy [28].

6. APPLICATIONS OF FDDS

6.1. Site-specific drug delivery and Increased Bioavailability

FDDS is the method of choice for drugs (such as furosemide and riboflavin) having absorption window in the upper small intestine. The absorption of furosemide has been found to be site-specific, i.e. it is mainly absorbed from the stomach which makes it good candidate for FDDS. This led to the development of a monolithic floating dosage form for furosemide which increased the GRT of the drug and hence its bioavailability [29].

6.2. Sustained drug delivery and reduced dosing frequency
Drugs having short biological half life are released in a sustained manner by use of FDDS. This results in flip-flop pharmacokinetics and facilitates a reduced dosing frequency. For example, levodopa when formulated as HBS, was found to be released and absorbed over a period of 4-5 h, maintaining significant plasma concentrations for 6-8 h. [29]

6.3. Targeted delivery to the upper GIT

FDDS serves as a targeted delivery for local ailments in the upper part of GIT like chronic gastritis, peptic ulcers, duodenal ulcers etc. The treatment involves high drug concentrations to be maintained at the site of action i.e. within the gastric mucosa. Because of their capability to float, the gastric residence time of the system can be increased for long duration and thus targeting the drug to the desired site [30].

6.4. Reduced fluctuations in plasma concentration

Continuous release of the drug from a controlled release floating delivery system gives drug plasma concentration within a narrower range as compared to the conventional dosage forms. As a result, concentration dependent adverse effects can be reduced. This attribute is especially useful for drugs with narrow therapeutic index [31].

6.5. Enhanced selectivity in pharmacological effect

There are some drugs that activate different types of receptors at different concentrations. FDDS has the property to minimize fluctuations in plasma concentration and thereby help to obtain certain selectivity in the elicited pharmacological effect of drugs [32].

7. CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure due to various physiological problems that limit the success of oral controlled DDS. Prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS comes across as an attractive approach to overcome these problems. However, the formulation parameters do play an important role in release of drug from the system. Drug-to-polymer ratio is the major factor affecting the floating time and the release properties of FDDS. The currently available polymer mediated non-effervescent and effervescent FDDS are designed on the basis of delayed gastric emptying and buoyancy principles respectively. Both appear to be an equally effective in modulation of controlled oral drug delivery.
AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS: Declared none.

REFERENCES


## Table 1: Examples of drugs explored for various floating dosage form [11]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Floating Dosage Form</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tablets/Pills</td>
<td>Riboflavin-5’-phosphate, Isosorbide dinitrate, Losartan Potassium,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p-Aminobenzoic acid, Quinidine gluconate, Amoxicillin trihydrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ditiazem, Fluorouracil, Sotalol, Theophylline, Chlorpheneramine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>maleate, Verapamil, Atenolol, Piretinide, Pentoxyfylne, Furosemide,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Captopril, Cisapride</td>
</tr>
<tr>
<td>2.</td>
<td>Capsules</td>
<td>Chloradiazepoxide HCl, L-dopa and beneserezide, Propanolol HCl,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salbutamol Sulphate, Misoprostol, Furosemide, Ursodeoxycholic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>acid, Seriotopeptidase</td>
</tr>
<tr>
<td>3.</td>
<td>Microspheres/</td>
<td>Tranilast, Asprin, griseofulvin and p-nitroaniline, Terfenadine,</td>
</tr>
<tr>
<td></td>
<td>Microballoons</td>
<td>Theophylline, Melatonin, Piroxicam</td>
</tr>
<tr>
<td>4.</td>
<td>Granules</td>
<td>Indomethacin, Prednisolone, Diclofenac sodium</td>
</tr>
<tr>
<td>5.</td>
<td>Films</td>
<td>Cinnarinze</td>
</tr>
<tr>
<td>6.</td>
<td>Powders</td>
<td>Several basic drugs</td>
</tr>
</tbody>
</table>

### Polymers
- HPMC 4000, HPMC 100, HPMC K4M, CMC, PVA, Calcium alginate, Carbopol, Ethyl cellulose, Eudragit RS and RL, acrylic polymer
- Ethyl cellulose
Table 2: Polymers used in preparations of GRDDS [14]

<table>
<thead>
<tr>
<th>Category</th>
<th>Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Release rate accelerants</td>
<td>Mannitol, Lactose</td>
</tr>
<tr>
<td>Release rate retardants</td>
<td>Magnesium Stearate, Dicalcium phosphate, Talc</td>
</tr>
<tr>
<td>Low density materials</td>
<td>Polypropylene foam powder</td>
</tr>
<tr>
<td>Inert fatty materials</td>
<td>Fatty acids, Bees wax,</td>
</tr>
<tr>
<td>Effervescent agents</td>
<td>Tartaric acid, Citric acid, Sodium bicarbonate, Citroglycine</td>
</tr>
</tbody>
</table>

Fig. 1. Anatomy of Stomach
Fig. 2. Schematic presentation of the structure of the low density foam powder, drug, and optionally, filler.
Fig.3. (a): A multiple-unit oral floating dosage system (b): Stages of Floating Mechanism: (1) Penetration of water; (2) Generation of CO$_2$ and floating; (3) Release of drug.