



Journal of Applied Pharmaceutical Research
 Volume 7, Issue 3, Year of Publication 2019, Page 1 – 8
 DOI: 10.18231/j.joapr.2019.003



Review Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | JOAPR

www.japtronline.com

ISSN: 2348 – 0335

FLOATING DRUG DELIVERY SYSTEM: AN OUTLOOK

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Article Information

Received: 12th October 2018

Revised: 26th April 2019

Accepted: 21st May 2019

Keywords

Drug delivery system, Floating, Gastric residence time

ABSTRACT

Floating drug delivery is considered as the most effective amongst the several approaches of gastro retentive drug delivery systems. The short gastric residence times (GRT) and unpredictable gastric emptying times (GET) are the two most important parameters that play a vital role in improving the bioavailability of drugs those are having an absorption window at the stomach. The floating drug delivery approach is a low-density system that may be effervescent or Non-Effervescent type with sufficient buoyancy to flow over the gastric contents and remain buoyant in the stomach without affecting the stomachic emptying rate for a prolonged duration. Floating dosage forms include tablets, granules, capsules, microspheres, microparticle, etc. are few formulations available commercially. A comprehensive summary of different floating drug delivery and its present status has been highlighted in this review.

INTRODUCTION

The oral route drug administration gained its popularities due to some of the unique features includes the reasonable cost of therapy, ease of administration, better patient compliance and acceptability, good range of available dosage form [1,2]. Despite certain diversity, the oral route of drug delivery has several limitations to deliver the drug in the upper part of GIT [3]. It is reported the drug induces orally may take 1 to 2 hours to move away from the stomach region to intestine whereas, it spend 14-24 hours inside intestine [4,5]. As a result, drugs especially those are having absorption windows in the stomach face serious bioavailability issues due to short residence time [6-7].

It is evident from the reported literature that growing interest has been observed in the development of oral Controlled release dosage forms that capable to deliver the drug at a predetermined rate for a prolonged period of time. Floating drug delivery systems (FDDS) is one, amongst the several approaches that are likely used in prolongation of the gastric residence times (GRT) [8,9].

There are numerous drug substances available that may get benefit from prolonged GI passage times or stomach residence time and consequently, the bioavailability and the therapeutic efficacy may improve that ultimately leads to a reduction of dosage frequency and improve patient compliance.

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Drugs that are absorbed from the stomach include antacids, antibiotics albuterol, chlorthalidone, are rapidly absorbed from GIT [12-13]. Drugs having low bioavailability e.g.- ranitidine, misoprostol, and drugs which are poorly soluble in intestinal pH e.g.- diazepam, dipyridamole is also reported to show good response as FDDS [14]. It releases at the site of absorption and thus enhanced bioavailability.

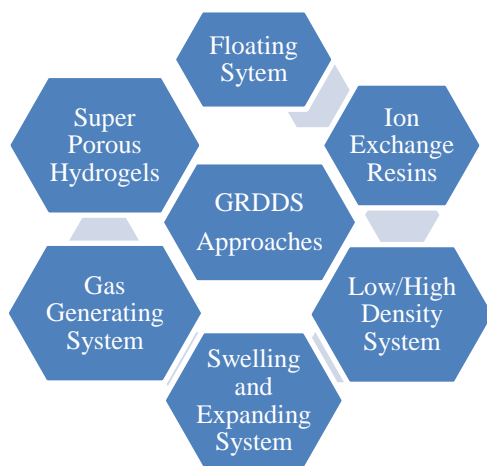


Figure 1: Approaches for gastro retentive drug delivery system

TYPES OF FDDS

Based on the mechanism of buoyancy, FDDS can be divided into two distinct types:

1. Effervescent system
2. Non-effervescent system

1. Effervescent System: The effervescent system also known as gas generating system that fabricated using gas generating agents include carbonates (sodium bicarbonate), organic acids (citric acid, tartaric acid) that together will generate carbon dioxide gas [15-16]. The generation of carbon dioxide reduces the density of the dosage form that helps to float the system in the stomach thus increase GI retention time. This system is further classified into two types – Volatile liquid containing system and gas generating system.

- a. **The volatile liquid containing system:** This system may be composed of volatile liquids like ether, cyclopentane etc
 - b. **Gas generating system:** This system mainly involves the use of agents which release carbon dioxide after a chemical reaction. Agents like sodium bicarbonate, citric acid, tartaric acid, chitosan, etc. are mainly used for this purpose.
- 2. Non-Effervescent System:** This system mainly composed of low density polymers that increase the effective surface area for the dosage form and allow the dosage form to float

for an extended duration. Generally gel-forming or extremely swellable polysaccharide, sort hydrocolloids, matrix-forming materials such as polycarbonate, polyacrylate, polystyrene, and bio-adhesive materials such as chitosan and Carbopol may be used in this system [17-18]

Table 1: Advantages and disadvantages of Floating drug delivery system [13-16]

Advantages

1. FDDS enhances the bioavailability of drugs those having an absorption window in the stomach.
2. FDDS minimizes the adverse effect of drugs on the colon
3. FDDS also reduces the counter activity of the body leading to higher drug efficacy.
4. The FDDS is helpful for the drugs which are absorbed in the proximal part of the small intestine.
5. FDDS is advantageous for locally acting drugs in the stomach.
6. FDDS improves gastric residence time hence drug absorption is also improved.

Disadvantages

1. Sufficient stomach fluid is required for effective treatment.
2. The drugs that undergoes high first-pass metabolism is not a suitable candidate for the purpose.
3. Drugs that produce gastric irritation are not suitable
4. Drugs having low aqueous solubility & stability problems in the GI tract are also not suitable candidates for FDDS
5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates.

PHYSIOLOGY OF STOMACH

The stomach is mainly divided into 3 regions: fundus, body, and antrum. The process of storing and digestion of food occurs within these regions. The gastric emptying occurs both during fasting state and feed state but the pattern of motility differ in both of these states [16,19]. The GI motility of the stomach consists of two modes, include inter-digestive motility and digestive motility. In a fasting state, a series of electrical events take place which cycle in the stomach and small intestine in every 2 to 3 hours. This cycle is called an inter-digestive myoelectric cycle (IMC) or migrating myoelectric cycle (MMC) [20]. Each cycle lasts for 90 to 120 min and consists of four phases as described by Wilson and Washington [21].

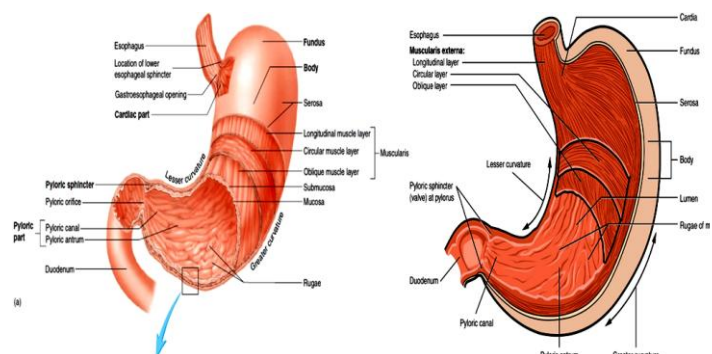


Fig 1: Structural configuration of stomach

A full cycle begins in the lower esophageal sphincter and finished in the ileum. The phases of the cycle are as follows-

- a) **Phase 1:** In this phase, the gastric emptying rate is slow as the onset of MMC is delayed. This phase usually lasts for 30 to 60 min. Contraction does not occur in this phase. It is also known as the basal phase.
- b) **Phase 2:** In this phase bile secretion and mucus discharge take place and intermediate contraction occurs. It lasts for 20 to 40 min. It is also known as the pre-burst phase. The intensity and frequency increase gradually as the phase progresses.
- c) **Phase 3:** In this phase, regular and intense contraction takes place for a short time. It last usually for 10 to 20 min. This phase is also called a housekeeper wave as it tends to empty the fasting contents of the stomach. Large objectives remain in the stomach in the fed state but passed down to the small intestine during this phase.
- d) **Phase 4:** This is the intermediate state between phase 3 and 1. It lasts from 0 to 5 min

FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS

Factors that affect gastric emptying time are as follows-

1. **Effects of dosage form size and shape:** Small size solid dosage form is generally expelled from the stomach during the digestive phase while the large size follows housekeeping wave phase. It is found that floating units have large GRT than the non-floating unit. The tetrahedron and ring-shaped matters have a better GRT as compared with other shapes [22].
2. **Gender, posture and age:** Women are having lower gastric emptying rates than men. In the case of an elderly person, gastric emptying time is slowed down especially in the case of a person above 70 years [22].

3. **Effect of food and specific gravity:** Low-density dosage form shows a higher duration of floating and comparatively slow gastric emptying rate. Several reported literature states that the intake of food is the main determinant in gastric emptying rate [23]
4. **Nature of meal and frequency of food:** The rate of the gastric emptying time mainly depends on the volume, viscosity and calorie content of meals. Feeding of indigestible material or fatty acid can change the motility pattern of the stomach. It can increase the gastric emptying rate and prolong the release of the drug. A protein-rich diet can increase GRT by 4-10 hours [23]
5. **Diseases State:** Diseases like Diabetes, Chron's disease, etc. can alter the gastric emptying time. Depression slows the gastric emptying time while stress increases the rate
6. **Effect of drugs:** Drugs like atropine, glycopyrrolate, metoclopramide, domperidone, etc increases the gastric emptying time while anti-cholinesterase drug-like neostigmine decreases the gastric emptying rate.
7. **State of the drug:** A demonstration using a radio labeled technique shows that the rate of gastric emptying time differs between liquid, digestible solid & indigestible solid.
8. **Formulation parameters:** Multi-particulate formulations show a better gastric emptying pattern than the single unit formulations.

COMPONENTS OF FDDS

Following components are used in the formulation of FDDS-

Hydrocolloids- Hydrocolloids are synthetic, anionic or non-ionic slightly modified cellulose derivatives e.g. - acacia, pectin, agar, gelatin, bentonite etc [24]

Polymers- Polymers like HPMC K4M, HPMC K15M, HPMC K100M, polyethylene glycol, polycarbonate, sodium alginate, PVA, PVP, eudragit, carbopol, methyl methacrylate, acrylic polymers are mostly used for the development of floating drug delivery [25-26]

Effervescent agent- Sodium bicarbonate, citric acid, tartaric acid, nitroglycerin, Di-sodium glycine carbonate etc. are used as an effervescent agent in the preparation of effervescent based floating formulation [27]

Inert fatty materials- Fatty materials have a specific gravity less than one which decreases the hydrophilic property and hence increased buoyancy. E.g. Beeswax, fatty acid, long-chain alcohol, mineral oil [27]

Release rate modifier - The release rate of the formulation can be modified by using excipients like lactose, mannitol [18,27].

Release rate retardants – They decrease the solubility hence retard the release rate of medicaments. E.g.- dicalcium phosphate, talc, Mg stearate[18].

Buoyancy increasing agent- Materials like ethyl cellulose which has a low bulk density less than one can be used for increasing the buoyancy of the formulation. It may be present with 80% of the weight[18].

Low-density material – They are used if necessary to decrease the weight of the formulation for them to float e.g.- Polypropylene foam powder.

Miscellaneous – Adjuvant like preservatives, stabilizers, lubricants, binders, etc can be used in the formulation as per requirements.

CHARACTERIZATION

Most of the reported floating formulation is either a single unit type (Tablet) or multi-unit type (microspheres/ microcapsule/ microbeads) of preparation. Therefore, the characterization of both the type are discussed chronologically as follows

Pre-compression study (single unit dosage form):

Compatibility studies between drugs and excipients: The physical compatibility study of drug and excipients are carried out to determine the possible physicochemical interactions. The study can be performed using FTIR, DSC or X-Ray diffraction technique [29].

Angle of Repose: In this study accurately weighed mixture of powder/granules/microparticles are placed in a funnel. The funnel may be adjusted in such a way that the tip of the funnel just touches the apex of the heap of blends. The blends are allowed to flow through the funnel freely on a horizontal surface. The diameter of the speeded mass (powder/granules/microparticles) will be measure, and the angle of repose can be determined by using the following equation [30].

$$\tan \theta = \frac{h}{r}$$

Where, θ = angle of repose, h = height in cm, r =radius in cm.

Bulk density

Apparent bulk density was measured by pouring the pre-weighted blend of powder into a graduated cylinder. The bulk volume of the blend was determined, and then the bulk density may be calculated by using the formula.

$$\text{Bulk Density} = \frac{\text{mass of the powder}}{\text{volume of the powder}}$$

Tapped density

The measuring cylinder containing a known mass of blend is tapped for a fixed duration of time and from a specific height as per standard protocol. The initial volume occupied in the cylinder is measured and the same processes are applied after tapping. The tapped density may be calculated by using the following formula

$$\text{Tapped Density} = \frac{\text{Mass of powder}}{\text{volume of powder after tapping}}$$

Carr's index (I): The compressibility index can be determined from the value of bulk and tapped densities[32]. The percentage compressibility of the bulk drug can be determined using the following formula. It is expressed in percentage -

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Hausner ratio: Hausner ratio can be calculated by the formula: Hausner ratio = Tapped Density/ Bulk Density

Post-compression parameters:

The single unit floating dosage form (tablet) can be subjected to quality control tests like weight variation, hardness, thickness, friability, and content uniformity.

Determination of hardness:

The hardness of the tablet is determined by using Monsanto or Pfizer Hardness tester. The tablets are placed between two loads, adjusted with a spindle, and the pressure required to break the tablets are measure. The average value of 3 tablets may be noted.

Disintegration Time: In-Vitro disintegration time can be determined by using the disintegration test apparatus. For this, the tablet is placed in each of the six tubes of the apparatus and one disc is added to each tube. The time taken for the complete disintegration of the tablet is measured.

Determination of friability

Roche friabilator may be used to perform the study. Previously weighted 20 matrix tablets may be placed in the friabilator and rotation speed and duration of rotation may be set as per the standard protocol. After completion of the rotation, tablets are taken out from the machine and reweighted, the difference is noted as per the following formula

$$F = 100 (1 - w_0 / w)$$

Determination of weight variation

Around 20 tablets were selected at random and weight accurately. Now, the average weight of the tablets may be

calculated. Then the deviation of individual weight from the total weight will be calculated. The obtained result will be compared with the given standard limits as per IP.

Determination of thickness of tablets

The thickness of tablets can be determined using slide calipers. The average thickness of five individual tablets may be reported as the thickness of the prepared tablet.

Determination of drug content in tablets

Randomly 3 tablets from each batch are selected and transfer to a 100 ml volumetric flask contain suitable medium. Store the content for 48 hours then took 1ml from each of the volumetric flasks and transfer to the test tube. The collected samples are analyzed after suitable dilution using a UV spectrophotometer at a suitable wavelength. The linearity equation obtained from the calibration curve is used for the estimation of drug content [34-35].

Tablet Dimensions: Thickness and diameter of tablets can be measured using a vernier caliper. Three tablets of each formulation are picked randomly and the dimension is determined. It is expressed in mm[35].

Buoyancy studies: In this study, the onset time of floating and duration of floating are measured. Randomly selected tablets are placed in a 250 ml beaker, containing 200 ml of 0.1 N HCl. The time required for the tablet to rise at the surface and the entire duration of time of tablet remain floated is determined[36].

Swelling study: The swelling index can be determined by placing the tablets separately in a glass beaker containing pH 1.2 HCl buffer and incubated at regular 1-hr time intervals until 24 hrs. The floating tablets are removed from beaker, and the excess surface liquid is removed carefully using the % swelling index (SI) and is calculated using the following formula[36-37]:

$$\text{Swelling Index (SI \%)} = \frac{W_t - W_0}{W_0} \times 100$$

In Vitro Dissolution Studies: The *in vitro* dissolution study may be performed by using a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 100 rpm. The dissolution test is performed using 900 ml of 0.1N HCl at 37°C ± 0.5°C. A sample (10 ml) of the solution is withdrawn from the dissolution apparatus at predetermined time intervals for 24 hrs and the samples were replaced with pre-warmed fresh dissolution media. The samples are filtered through a Whatman filter paper and diluted to a suitable concentration with 0.1 N HCl as a blank. The absorbance of the

solution is measured at 276 nm using a UV spectrophotometer [6,38].

Evaluation of multi-unit type floating microspheres:

The above-mentioned studies that refer for single unit dosage form like compatibility studies, buoyancy studies, micromeritics properties like angle of repose, bulk density, tap density, carr's index, Hausner ratio are also applicable for multiunit floating formulations. Other important evaluations for multiunit floating dosage form are mentioned as follows

Percentage yield (%): The percentage yield of floating microspheres can be measure by dividing the actual weight of the product by the total amount of all non-volatile components. Following formula may be used to calculate

$$\% \text{ yield} = \frac{\text{Weight of floating microsphere}}{\text{Weight of drug and polymer}} \times 100$$

Determination of Particle size: Particle size and shape of the microspheres are determined by the microscopic method. Microspheres to be examined are placed under a microscope and the size of individual particles is determined using eyepiece micrometer and stage micrometer. Average particle size is measured and reported

Drug entrapment efficiency: Drug entrapment efficiency of microspheres may be performed by accurately weighing a certain amount of microspheres and crushing them properly using mortar and pestle. Then the crushed matter shall be suspended in the predetermined quantity of acid buffer and kept aside for 24 hours. After that, the content subjected to filtration and the filtrate is analyzed spectrophotometrically at a suitable wavelength. The percent of drug entrapped shall be calculated as follows:

$$\text{Entrapment efficiency} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \times 100$$

Surface morphology: The surface morphology was measured by using a scanning electron microscope (SEM).

In-vitro drug release study:

The *in-vitro* drug release may be carried out by using the dissolution test apparatus. Either a single tablet or floating microspheres are placed inside a dissolution apparatus. The study shall be carried out under a set of standard conditions. Throughout the study, the sink condition needs to be maintained and around 5 ml sample required to be transferred after a fixed time interval. The collected samples are analyzed under a UV spectrophotometer after suitable dilution. The amount of drug release may be calculated based on the obtained data [42].

FUTURE PERSPECTIVE OF FDDS:

Floating drug delivery is a potential approach and became a vital aspect of research for forthcoming era. Drugs that are having poor bioavailability owing to their restricted absorption in the upper gastrointestinal tract are effectively delivered through the floating delivery approach. However, several issues associated with the rational development of FDDS with the

fasted and feed states are still under consideration [43]. The FDDS reduces fluctuations in the plasma level of drug results from delayed gastric emptying. The floating concept can also be utilized in the development of various anti-reflux formulations and these may play a potential role to treat Parkinson's disease.

MARKETED FORMULATIONS OF FDDS**Table 2: Commercially available floating drug delivery system**

Brand name	Delivery system	Drug	Company
Valrelease®	Floating capsule	Diazepam	Hoffmann-LaRoche
Madopar® HBS (Prolopa® HBS)	Floating, CR capsule	Benserazide and L-Dopa	Roche Products, USA
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide, Mg Carbonate	GlaxoSmithKline, India
CifranOD ®	Gas-generating floating form	Ciprofloxacin	Ranbaxy, India
Convicon®	The colloidal gel-forming FDDS	Ferrous sulfate	Ranbaxy, India
Topalkan®	Floating liquid alginate preparation	Al – Mg antacid	Pierre Fabre Drug, France
Cytotech®	Bilayer floating capsule	Misoprostol	Pharmacia, USA

Table 3: List of Patents on Floating Drug Delivery System

Title	Patent Number	Date	Inventors	Ref
Gastric floating system	WO02/102415A1	27 Dec 2002	Avachat MK., Dhamne AG.	[44]
Floating drug delivery composition	WO01/58424A1	16 Aug 2001	Watts PJ, Smith A, Bond JR and Lafferty WCI	[45]
Gastro retentive drug delivery system comprising an extruded hydratable polymer	WO03/105812A1	24 Dec 2003	Hassan M	[46]
Gastro-retentive drug delivery system	WO2014/014348A1	23 Jan 2014	Meijerink HJC, Changoer L, Blom W, Visser MR, Frijlink HW, Eissens AC	[47]
Gastroretentive drug formulation & delivery systems and their method of preparation using functionalized calcium carbonate	WO2014/057026A1	17 Apr 2014	Gerard DE., Schoelkopf J, Gane P.A.C, Eberle VA, Alles R, Puchkov M and Huwyler J	[48]

CONCLUSION

Floating drug delivery system (FDDS) is a popular concept comes under gastro retentive drug delivery that effectively delivers the drug in the upper part of GIT. Drug molecules that are having an abortion window in the stomach can be safely delivered through this route. This drug delivery approach has gained considerable popularity as per patient acceptability and compliance is a concern.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

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