

Review Article

THERAPEUTIC PROSPECTS OF GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEM: A REVIEW

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ARTICLE INFO

Received 14 February 2020

Revised 18 July 2020

Accepted 28 August 2020

Keywords:

- Gastrointestinal tract
- Gastroretentive time
- Gastroretentive drug delivery systems
- Floating drug-delivery systems
- Controlled
- Prolonged drug release

ABSTRACT

The delivery of conventional drugs through oral route mostly exhibits a major limitation of poor bioavailability. Such drugs have a narrow absorption window in the gastrointestinal tract (GIT) is due to poor bioavailability. Also, some others limitations, including incomplete drug release and short residence time at the site of absorption are associated with such drugs. So, to overcome the limitations and to increase the oral absorption of these drugs, gastroretentive drug delivery systems (GRDDS) have been established. The GRDDS enables delivery of incorporated drugs in a controlled manner and also prolongs the drug release in GIT. Apart from GRDDS, floating drug-delivery systems (FDDS) have also exhibited the competence to put up these alterations with no impacts over the drug release. This review primarily emphasizes on different physiological concerns associated with gastroretentive-FDDS (G-FDDS), and focuses on current scientific progresses. Also, recent literatures with distinctive focus on the mechanism of floatation and gastric retaining abilities have been explored in this review. Further, various important factors associated with FDDS, including classification, advantages, limitations and evaluations parameters has also been discussed.

1. INTRODUCTION

Oral route of drug administration exhibits few sequential steps such as, initial entry of drug into the abdominal fluid, followed by further degradation through proper metabolism. The main purpose of FDDS is to attain a buoyant system which could be efficiently achieved by making the dosage form less dense as compared to the gastric fluid. However, numerous complications such as gastric emptying, poor solubility, poor bioavailability and others, have been reported which hinder the retaining of drug or dosage forms in the gastric fluid leading to less release of drug in the GIT. So, to uphold the drug release from the dosage form in the GIT, it is very important to modify these systems to increase drug solubility, bioavailability and residual time with low toxicity [1].

Currently various approaches, including mucoadhesive systems, hydrogels, raft forming systems, lower density systems, swelling and elastic systems, magnetic systems, and floating dosage form, have been reported to upsurge the gastric retaining of the drugs. Apart from these, the floating tablets also play significant role. These systems are mainly matrix type systems which comprises the drug in the matrix core which further interacts with the gastric fluid and the controlled drug release is obtained. GRDDS (Table 1 and Table 2) could persist in the gastric area for some hours and thus considerably prolongs the residual time of drugs in the GIT [2].

1.1. General physiology of GIT

Physiologically the stomach is distributed into three sections, the fundus, body and antrum (pylorus) (Fig. 1). The proximal part

composed of fundus and body assists as a reservoir for undigested constituents, whereas the antrum is the main spot for mixing motions and act as a pump for gastric evacuating by impelling actions. Gastric emptying has been observed both in the fast and fed conditions. An inter-digestive cycle of electric-chemical procedures has been observed during the fasting conditions in the abdominal and intestinal regions with a repetition in 2-3 hours and is described as migrating myoelectric cycle (MMC). This cycle is further categorized into four phases (Fig. 2) [3].

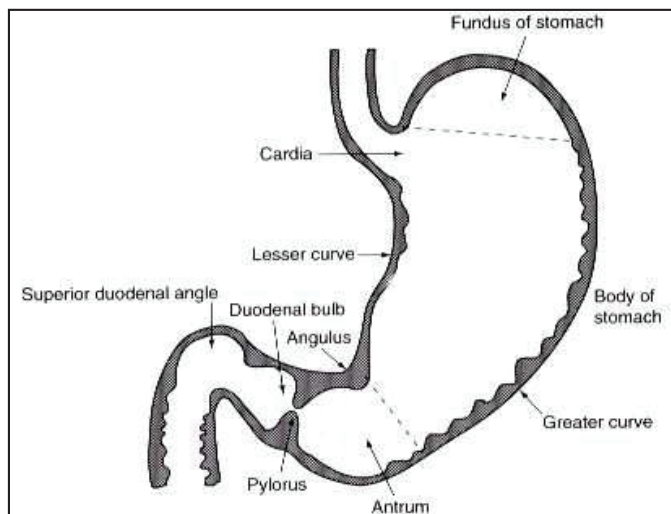


Fig. 1: Schematic representation of stomach and its associated parts

- **Phase I (Basic phase)** – lasts from 30-60 min. with unusual contractions.
- **Phase II (Pre-burst phase)** – lasts for 20-40 min. with recurrent action potentials and contractions.
- **Phase III (Burst phase)** – lasts for 10-20 min which comprises intense and consistent contractions for shorter durations.
- **Phase IV** - lasts 0-5 min & arises between phase 2 and 1, in 2 consecutive cycles. [4]

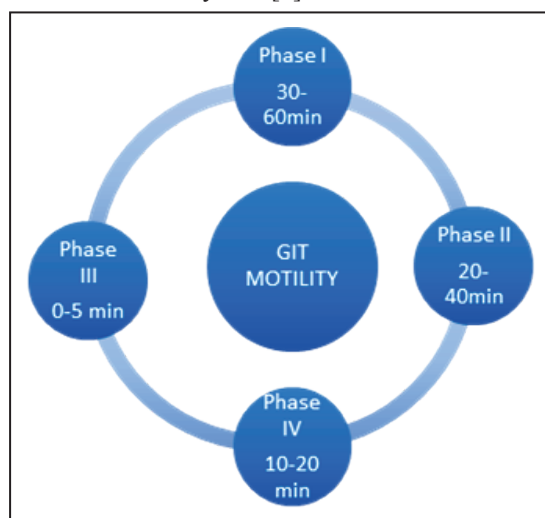


Fig. 2: Schematic representation of GIT motility and involved phases

Table 1: Ideal candidates of GRDDS [5, 6]

S. No.	Drugs	Examples
1.	Narrow absorption window in GIT	L-DOPA, p-aminobenzoic acid.
2.	Locally active in the stomach	Misoprostol, antacids.
3.	Unstable in the intestinal or colonic environment.	Captopril, ranitidine, metronidazole.
4.	Disturb normal colonic microbes	Antibiotic used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin.
5.	Exhibit low solubility at high pH values.	Diazepam, chloridiazepoxide, verapamil.

Table 2: Factors affecting of GRDDS [7-12]

S. No.	Factors	Ideal conditions
1.	Particle size	Should be range in the 1-2 mm.
2.	Density	Should be range of the dosages form 1 g/cm ³ to 2.5 g/cm ³ .
3.	Size & shape of dosages form	Size of dosages form should be greater than 7.5 mm in diameter & shape of dosages form should be ring & tetrahedron devices with flexural.
4.	Single unit/multiple unit	Multiple units are preferable because of predictable release profile, co-administration of different units, larger safety margins.
5.	Food intake	Gastric retention times is longer in fed states.
6.	Nature, caloric content	Indigestible polymers, fatty acid salts, increase caloric content, increase acidity increases gastric retention time, fat & protein meal increases GRT.
7.	Frequency of intake	Gastric retention time increases 400 times & due to low frequency of MMC.
8.	Posture	Varies between spine & upright ambulatory states.
9.	Gender	Males have greater GRT than females.
10.	Age	70 shows longer GRT
11.	Nature of drug	Drug with impaction GIT (Codeine and pharmacokinetic agents)
12.	Other factors	Body mass index, physical activity, molecular weight, lipophilicity of the drug.

2. FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery system (FDDS), also recognized as hydrodynamically balanced system (HBS), have a bit lesser density than that of the gastric fluids and due to buoyancy mechanism, floats in the stomach devoid of any disturbances in the rate of gastrointestinal emptying for a prolonged duration. FDDS allows the drug to float in the pyloric region and thus allows slow release of the drug with the desired rate. After the drug is released, the remaining system is evacuated from the stomach. This causes improvement in the gastroretentive time and an enhanced control in the plasma drug concentration variations [13,14].

2.1 Advantages of FDDS

- Improves patient compliance by reduced dosing frequency.
- Drug with less half-life could be provided to give prolong activity.
- Gastroretentive time of the drug is improved.
- Prolong drug release pattern is observed with a controlled manner.
- Improved absorption of drugs that only dissolve in the stomach.
- Release of drugs for local action in the abdomen. [15,16]

2.2 Limitations of FDDS

- Drugs belonging to NSAID category could cause gastric injuries and slow the drug release in the stomach or GIT.
- Drugs such as isosorbide dinitrate that are evenly absorbed throughout the GIT would not benefit from inclusion in the gastric retention system.
- The greater throughput of bio adhesion and mucus in the acidic environment might raise queries on the efficacy of FDDS.
- Physical integrity of the system is very crucial and primary prerequisite for the accomplishment of the system.
- Higher inconsistency in the gastric emptying time is monitored due to deviations in the emptying procedure [17].

2.3 Classification of FDDS

FDDS are broadly categorized into three subtypes and has been demonstrated in figure 3.

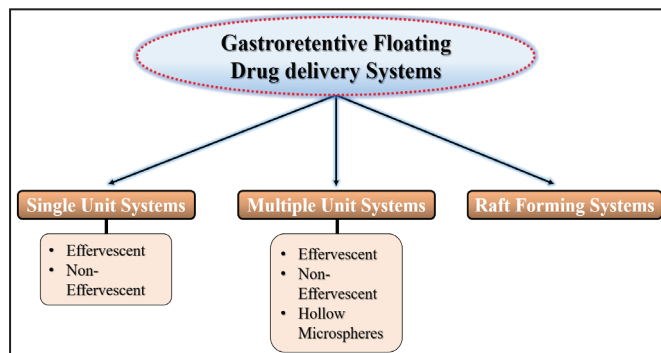


Fig. 4: Various type of GRDDS based on their mechanism.

2.3.1 Single unit floating dosage system

These systems are one of the most robust and easiest method but have limited uses due to menace of losing their impacts too early due to their minimal evacuating from the stomach. So, they might cause high inconsistency in bioavailability and local exasperations in the GIT due to over release of drug at particular sites [18]. Single unit floating dosages form are two types-

i. Effervescent Systems (Gas-generating Systems)

These are the matrix type of system which are usually prepared with the help of swell able polymers such as methyl cellulose and chitosan, and several other constituents like, sodium bicarbonate, citric acid, tartaric acid and others. Generally, they are prepared in such a way that when it comes in contact with the gastric contents (acidic), carbon dioxide (CO₂) is released, causing entrapment in swollen hydrocolloids, thus provides buoyancy for delivery systems [19].

ii. Non-effervescent Systems

Non-effervescent floating dosages systems appears to be as gel, usually formed with the help of polymers (swellable cellulose type hydrocolloids) like polycarbonate, polyacrylate and polystyrene. Such delivery systems are prepared mixing of drug and gel or drug and hydrocolloids. When these systems come into contact with the gastric fluids they make a swelling type dosage form and formed gel-like structures [20].

2.3.2 Multiple Unit Floating Dosage Systems

Single unit formulations are associated with the concerns such as sticking mutually or being congested in GIT, which might cause irritation in the GIT. Multiple unit systems keep away from gastric emptying behaviour of single unit systems. It decreases the inter difficulty inconsistency in absorption and the chances of dose dumping is least. Further more, the multiple unit dosages systems are categorized into three subtypes.

i. Effervescent system

Usually, these systems comprise of calcium alginate core and calcium alginate/ polyvinyl alcohol (PVA) membrane, prepared in the separated air compartments. The presence of water upsurge the percolation rate from the PVA and enhances the membrane permeability, maintains the reliability of the air compartments. Freeze-drying method is also used to prepare the floating calcium alginate beads. In this formulation, the sodium alginate (SA) solution is added drop wise into the aqueous solution of calcium chloride and the beads were obtained after freeze-drying. The results showed that in case of floating beads the gastric residence time was prolonged for more than 5.5 hours, whereas the non-floating beads exhibited a shorter gastric residence time.

ii. Non-effervescent system

In this systems as compared to the effervescent type, the system containing indomethacin using chitosan polymeric

excipient was more effective. The multiple unit systems containing indomethacin as model drug was prepared through extrusion process in which the mixture of drug, chitosan and acetic acid was extruded through needle. The extrude was cut and dried chitosan hydrates floated in the acidic media, releases required amount of drug and thus the modified drug polymer ratio was obtained[21].

iii. *Hollow microspheres*

The drug-loaded hollow microsphere systems with an outer polymer coat were prepared through a novel emulsion solvent-diffusion method. The ethanol/dichloromethane (DCM) solution, drug and enteric polymer was poured into agitated solution of PVA and was further thermally controlled at 400 °C. The gaseous phase was generated in the dispersed polymer droplets by the evaporation of DCM and internal cavity in the microspheres of the polymer with drug was developed[22].

2.3.3 *Raft forming system-*

In such systems, a gel-forming solution (e.g. SA solution containing carbonates) swells and an adhesive cohesive gel containing entrapped CO₂ bubbles are formed with an interaction with the gastric fluid. Formulations also typically contain antacids such as aluminum hydroxide or calcium carbonate to decrease gastric acidity. Because raft forming systems create a layer on the top of gastric fluids, they are regularly used for gastro-oesophageal reflux remedies [23].

2.4 *Mechanism of FDDS*

Numerous efforts have been made to preserve the therapeutic efficacy of the drug or the dosage form in the stomach or GIT, with an effort to increase the retention time of the drug. These efforts comprise lead to the establishment of FDDS, mucoadhesive systems, higher-density systems, altered shape systems etc. Among these, the FDDS are the most commonly used systems. The FDDS have a bulk density lesser than that of the gastric fluids, thus remains floating in the stomach without affecting the rate of gastric emptying for a prolonged duration. Though the FDDS is floating on the gastric substances, the drug is released gradually at the preferred rate from the system. After the drug is released, the remaining are emptied from the stomach. This improves the gastroretentive time of the drug or dosage forms and a regulates the plasma drug concentration. Additionally, a minimal gastric content chosen to permit the proper accomplishment of the buoyancy retention theory, a minimum level of floating force (F) is also essential to keep the dosage forms continually floating over the surface. To estimate the floating force kinetics, a novel tool has been reported. The tool functions by computing unremittingly the force equivalent to F (as a function of time) which is essential to preserve the sunken object. The object floats better if the values of 'F' are on the greater side. This apparatus assists to optimize the FDDS with respect to the stability and durability of the floating forces

developed in order to avoid the hitches of unexpected intra-gastric buoyancy ability differences.

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

Where, F = sum vertical force, D_f = fluid density, D_s = object density, v = volume and g = acceleration due to gravity.

Floating systems was initially demonstrated by Davis in 1968, and stated that the systems have bulk density lower than that of the gastric fluid, would remain floating in the stomach regions for prolonged duration[24, 25].

2.5 *Evaluation of FDDS*

2.5.1 *Size and Shape Evaluation*

Particle size and shape plays a vital role in identifying the solubility rate of drugs and possibly its bioavailability [26].

2.5.2 *Drug-excipient interaction*

Drug-excipient interaction studies are performed with the help of sophisticated instruments like FTIR (Fourier-Transform Infrared Spectroscopy) and HPLC (High Performance/Pressure Liquid Chromatography). The occurrence or disappearance of a new peak or older peak from the novel drug or excipient signifies any possible interaction of the drug with the excipients [27].

2.5.3 *Angle of repose*

The angle of repose is estimated by the funnel method and checked through the flow properties of the powder.

$$\tan \theta = h/rs$$

Where, h = height & r = radius of powder

2.5.4 *Weight variation test*

To access this test, generally 20 tablets are selected arbitrarily from every batch and weighed to check for any weight variations[28].

Weight variation = Final weight- initial weight / Final weight

2.5.5 *Bulk density*

Bulk density denotes to the total density of the material. It comprises interparticle spaces and the correct amount of intra particle pores. The packing of particles is mostly responsible for bulk density of the particle.

Bulk density = weight of powder blend/ untapped volume of the packing[29]

2.5.6 *Tapped density*

Tapped density is the relation of the total mass of the powder to the tapped volume of the powder.

Tapped density = weight of powder blend/ tapped volume of the packing [29,30]

2.5.7 Hausner's ratio

Hausner's ratio is determined by resulting from tapped density/ bulk density.

2.5.8 Carr's compressibility index

Compressibility index determine the tapped density – bulk density/ tapped density*100.[31]

2.5.9 Friability test

The friability test is performed with the help of friabilator apparatus. The friabilator is operated at 25 rpm for 4 min or run up to 100 revolutions. It is expressed in percentage %.

$$F(\%) = (1 - W_0/W) * 100$$

Where, W_0 = weight of the tablets by the test; W = weight of the tablets after test.

2.5.10 Hardness

Hardness test is determined by Monsanto hardness tester & it is expressed is kg/cm[32].

2.5.11 Floating Lag Time / Total Floating Time

The time among the start of the tablet merging into the medium and its augmentation to a upper one third of the dissolution container is termed as floating lag time and the time for which the dosage form floats is termed as the total floating time. These tests are usually accomplished in simulated gastric fluid (SGF), made up of 0.1 N HCl (900ml) maintained at 37°C (dissolution media), and study is performed in the USP dissolution apparatus.

2.5.12 Tablet swelling indices

Tablets are weighed (W_1) and set in a glass beaker, comprising of 0.1 N HCl (200 mL), conserved in a water bath ($37 \pm 0.5^\circ\text{C}$). At regular time intervals, the tablets were removed and the extra surface liquid was sensibly removed with help of a filter paper. The swollen tablets were then reweighed (W_2). The swelling index (SI) is calculated by the formula:

$$SI = (W_2 - W_1/W_1)$$

Where, W_2 = Final Weight; W_1 = Initial Weight

2.5.13 In vivo evaluations

This study is performed to measure the gastroretention of the drugs or dosage forms and is passed out through the means of X-ray or Gamma scintigraphy monitoring of the dosage form transition in the GIT.

2.5.14 Percentage drug entrapment

Percentage entrapment efficiency (%EE) is found to be as one of the most vital factors of the developed delivery systems. In this test, the drug is extracted by an apt process, analyzed and is calculated from:

$$PDF = \text{Practical drug loading} / \text{Theoretical drug loading} \times 100$$

2.5.15. In vitro floating ability (Buoyancy %)

The known quantity of microspheres are usually found swelled over the surface of a USP (Type II) dissolution apparatus filled with 0.1 N HCl (900 ml) and agitated at 100 rpm for 12 hours. After 12 hours, the floating and settled layers are separated, dried in a dissector and weighed.

$$2.5.16 \text{ Buoyancy } (\%) = (W_f / W_f + W_s) \times 100$$

Where, W_f and W_s are the weights of floating and total microspheres respectively[31,32].

2.5.17. In-vitro drug release

In-vitro release test is assessed by using USP II apparatus (paddle) with a RPM of 50 or 100 at room temperature in SGF (pH 1.2 without pepsin). Aliquots of the samples are collected in regular intervals and examined for the drug content. New methodologies as described in USP XXIII describes that the drug or dosage forms are permitted to sink to the bottom of the vessel before rotation of blade is started. A small loose piece of non-reactive material such as not further than a few turns of wire helix can be attach to these dosage units that would otherwise float[32].

3 CONCLUSION

Based on the literatures surveyed, it may be concluded drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. All these gastrointestinal drug delivery systems (high density, floating, expandable or swelling superporous, bioadhesive, and magnetic systems) are interesting and present their own advantages and disadvantages gastro retentive dosages forms are enhancing absolute bioavailability.

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