REVIEW ARTICLE

FLOATING DRUG DELIVERY SYSTEM: A INNOVATIVE APPROACH

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ABSTRACT

The current Pharmaceutical scenario focuses on the development of sustained drug delivery systems to achieve required therapeutic concentration with less amount of dose. Several approaches are currently utilized in the prolongation of the gastric residence time including floating drug delivery systems, swelling and expanding system, polymeric bio-adhesive systems, high density systems, modified-shape systems and other delayed gastric emptying devices. From the formulation and technological point of view, the floating drug delivery system is comparatively easy and logical approach. Floating drug delivery system is one amongst the GRDFs used to achieve prolonged gastric residence time (GRT). In this review the methods of evaluation of various floating dosage forms and applications of these systems are summarized.

Keywords: Floating drug delivery system (FDDS), Gastric residence time (GRT), Buoyancy

INTRODUCTION

Oral delivery of drugs is the most preferred route of drug delivery due to the ease of administration; low cost of therapy, patient compliance and flexibility in formulation etc.¹ So the design of oral control drug delivery systems (DDS) should be primarily aimed to achieve more predictable and increased bioavailability.² Nowadays most of the pharmaceutical scientist is involved in developing the ideal drug delivery system. This ideal system should have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Scientists have succeeded to develop a system and it encourages the scientists to develop control release systems. Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.^{3, 4} It is widely acknowledged that the extent of GIT drug absorption is related to contact time with the intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed.⁵ Gastro retentive systems can continue to exist in the gastric region for several hours and hence prolong the period of gastric residence time (GRT) of drugs. The basic idea behind the development of such type of a system, to maintain a constant level of drug in the blood plasma inspire of the fact that the drug dose not undergoes disintegration by which 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. Floating drug delivery systems (FDDS) are aimed to keep possession of the drug in the stomach and useful for poorly or unstable dosage form for those that are less or highly soluble and stable in intestinal

fluids.⁶ It is the formulation of a drug and gel forming hydrocolloids meant to remain buoyant on stomach contents. This not only prolongs GI residence time but also does so in an area of the GI tract that would maximize drug reaching its absorption site in solution and hence ready for absorption.⁷ The principal is very simple that the floating of the drug in the stomach occurs due to the low density of the dosage form. Prolonged gastric retention time improves bioavailability, reduces wastage of the drug and improves solubility of those drugs which are less soluble at high pH. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps in improving bioavailability of new products with improved therapeutic possibilities and substantial benefits for patients. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail.⁸

Basic Gastrointestinal Tract Physiology

Basically stomach divided into 3 regions:

1. **Fundus:** The fundus of the stomach is the left portion of the stomach's body, and is marked off from the remainder of the body by a plane passing horizontally through the cardiac orifice. The rounded part of the upper stomach allows for an accumulation of stomach gases produced by chemical digestion.
2. **Body:** It also called the **corpus** and it is an anatomical region of the stomach in humans.
3. **Antrum (pylorus):** The region of the stomach that connects to the duodenum is the pylorus. It has two parts, the pyloric antrum which connects to the body of the stomach, and the pyloric canal, which leads into the duodenum.

Figure 1 Physiology of Gastrointestinal Tract

The proximal part made of fundus and body acts as a reservoir for undigested material, the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.⁹ Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.¹⁰ This is called the inter-digestive migrating myoelectric cycle (MMC).

The inter-digestive migrating myoelectric cycle (MMC) is further divided into 4 phases as described by Wilson and Washington.¹¹

Phase I (basal phase) - lasts from 40 to 60 minutes with rare contractions.

Phase II (preburst phase) - lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (burst phase) - lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV - lasts for 0 to 5 minutes and occur between phases III and I of 2 consecutive cycles.

Figure 2: GI motility pattern

After the ingestion of a mixed meal, pattern of contractions changes from fasted state to fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state.

These contractions result in reducing the food particle size (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state, onset

of migrating myoelectric cycle (MMC) is delayed that results in slowing down of gastric emptying rate.^{1,12}

Scintigraphic studies determine the gastric emptying rates allow to be seen that orally administered GRDFs are subjected to basically two complications, first short gastric residence time and second unpredictable gastric emptying rate.

Classification of Floating Drug Delivery System⁸

A. Effervescent system

- Gas generating system
- Volatile liquid containing system

B. Non-effervescent System:

- Colloidal gel barrier system.
- Alginate beds.
- Hollow microspheres / Microballons.
- Intragastric Floating Drug Delivery Device / Microporous compartment system

Effervescent Floating Dosage Forms:

These are matrix types of systems prepared with the help of swellable polymers (methylcellulose and chitosan) and various effervescent compounds (sodium bicarbonate,

tartaric acid, and citric acid). They are formulated in such a way that when come in contact with acidic gastric contents, CO₂ liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms.^{13, 14}

Volatile liquid containing systems:

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid (like ether, cyclopentane), that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bio-erodible plug made up of PVA, Polyethylene, etc. that gradually dissolves and 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.^{15, 54}

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.^{2, 55}

Figure 3: Mechanism of floating of beads (GF=gastric fluid)

Non-effervescent Floating Dosage Forms:

The non-effervescent FDDS works on the mechanism of polymer swelling, bioadhesion of the polymer to mucosal layer of GI tract. The most commonly used excipients for the preparations of non-effervescent FDDS are gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes simple approach of thoroughly mixing of the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains bulk density of less than 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form, so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.^{13, 15, 16}

Colloidal gel barrier system:

A system that contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel forming highly swellable cellulose type hydrocolloids.e.g. HEC, HPMC, NaCMC, Polysaccharides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms.^{16, 54}

Alginate beads:

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution

of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40°C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours.^{15, 16}

Hollow microspheres / Microballons:

It is prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40°C . The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug.^{16, 17}

Intragastric / Microporous compartment system:

The system composed of a drug reservoir encapsulated in a microporous compartment having pores on top and bottom surfaces. The peripheral walls of the reservoir compartment were completely sealed to prevent any physical contact of the undissolved drug with walls of the stomach.^{17, 18} Novel levodopa gastro retentive dosage form based on unfolding polymeric membranes which combines extended dimensions with high rigidity. It was

folded into a large size gelatin capsules. In vitro studies showed that unfolded form reached within 15 minutes after administration and it was confirmed in vivo in beagle dogs. The unfolded form was maintained for at least 2 hours. It was concluded that this dosage form could improve therapy of different narrow absorption window drugs. However, there are possibilities of the polymeric films to get stuck in the esophagus causing extreme discomfort to the patient or drug related injuries and repeated administration of rigid dosage form may result in gastric obstruction.^{18, 19}

Figure 4: Intra-gastric floating drug delivery device

Table 1: Some materials used for formulation of FDDS

S. No.	Drugs	Polymers used	Ref
1.	Piroxicam	Eudragit S 100	20
2.	Cefpodoxime Proxetil	HPMC K15M, EC	21
3.	Furosemide	HPMC 4000, HPMC 100, CMC, Sodium alginate, Xanthum gum	22
4.	Ketoprofen	Eudragit RS and Eudragit RL	23
5.	Nimodipine	HPMC, PEG-6000, Polaxamer-188	24
6.	Ciprofloxacin	HPMC	25
7.	Para-amino benzoic acid	Polyvinyl acetate, Purified shellac	26
8.	Paracetamol	PVPK 30, Methyl Cellulose, HPMC (K4M, K15M, K100M)	27
9.	Cimetidine	HPMC, Ethyl Cellulose	28
10.	Theophylline	Methocel K100M, K15MCR	29
11.	Pentoxifylline	HPMC K4M, Sodium CMC, Ac-di-sol	30
12.	Verapamil	Cellulose acetate, Eudragit S 100, Acrycoat A 100	31
13.	Celiprolol Hydrochloride	HPMC (K4M, K15M, K100M), Ethyl Cellulose, Polyethylene oxide WSR-60K	32
14.	Metformin	HPMC K4M and Ethyl Cellulose	33
15.	Stolol Hydrochloride	Sodium carboxy methyl cellulose, Hydroxy propyl cellulose	34
16.	Famotidine	Methocel K4M, K15M	35
17.	Cephalexine	HPMC K4M, Xanthum gum, Guar gum, Microcrystalline cellulose	36
18.	Domperidone Maleate	Xanthum gum, Methocel K4M, K15M, K100LV	37
19.	Glipizide	Methocel K4M, Eudragit RS100	38
20.	Nimesulide	HPMC of low and high viscosity, Guar gum, carbapol	39

ADVANTAGES^{40, 41}

- Enhance Bioavailability
- Sustained drug delivery
- Reduce frequency of dosing
- Targeted therapy of local ailments in the upper GIT
- Reduce fluctuation of drug concentration
- Minimize adverse activity colon

DISADVANTAGES^{42, 43}

- Not feasible for those drugs that have solubility or stability problems in gastric fluids

- Not suitable for the drugs that are irritant to gastric mucosa
- This system requires sufficient high level of fluids in stomach, so that the drug dosage form float therein and work efficiently
- These systems also require the presence of food to delay their gastric emptying

EVALUATION^{18, 28, 44-52}

Determination of the Drug Content: It provides how much amount of the drug that was present in the formulation and should not exceed the limits acquired by

the standard monographs. Drug content was determined by using spectroscopy techniques HPLC, HPTLC methods, Micro titrimetric methods, Inductively Coupled Plasma Atomic Emission Spectrometer, Near infrared spectroscopy.

A. For Single Unit Dosage Forms (Tablet):

- **Floating lag time and total floating time:** It is the time taken by the tablet to emerge on the surface of dissolution medium and expressed in few seconds or minutes. For determination of floating lag time and total floating time, simulated gastric fluid or 0.1 mole.lit⁻¹ HCl (maintained at 37°C) and USP dissolution apparatus containing 900 ml of 0.1 molar HCl as dissolution medium is used.
- **In-vitro drug release and floating duration:** This is determined by using USP II apparatus (paddle) stirring on 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.
- **In-vivo evaluation:** This is carried out by means of X-ray or Gamma scintigraphic monitoring of the dosage form transition in the GIT.
- **Content uniformity, hardness, friability:** These tests are performed according to specified monographs.

B. For Multiple Unit Dosage Forms (beads, Microspheres):

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

- **Particle Size and shape:** Dimensional and morphological analysis is carried out with the aid of scanning electron microscopy (SEM), and size can also be measured by optical microscope.
- **% yield of beads:** This is calculated from the following formula.

$$\left(\frac{\text{Weight obtained}}{\text{Total weight of drug and polymer}} \right) \times 100$$

- **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 desiccator and weighed. The buoyancy is calculated from the following formula.

$$\left\{ \frac{W_f}{(W_f + W_s)} \right\} \times 100$$

Where W_f and W_s are the weights of floating microspheres and settled microspheres respectively.

- **Drug-excipient (DE) interactions:** This is done using FTIR. Appearance of a new peak, and/or disappearance of original drug or excipient peak indicate the drug excipient interaction. Apart from the above mentioned evaluation parameters, granules are also evaluated for the effect of ageing with the help of Differential Scanning Calorimeter or Hot stage polarizing microscopy.
- **Swelling studies:** This is performed to calculate molecular parameters of swollen polymers. It is

determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include Light scattering imaging (LSI), H₁NMR imaging, Confocal laser scanning microscopy (CLSM), etc. By using Dissolution apparatus (USP dissolution apparatus (USP-24) labindia disso 2000) it is calculated as per the following formula.

$$\text{Swelling ratio} = \frac{\text{Weight of wet formulation}}{\text{Weight of formulations}}$$

- **Entrapment efficiency:** The drug is extracted by a suitable method, analyzed and is calculated from the following formula.

$$\left(\frac{\text{Practical amount of drug present}}{\text{Theoretical drug content}} \right) \times 100$$

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS: ^{43, 54-55}

- **Enhance bioavailability:** The bioavailability of CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.
- **Sustained drug delivery:** Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents.⁴² These systems are relatively larger in size and passing from the pyloric opening is prohibited.^{9, 55}
- **Site-specific drug delivery systems:** These systems are particularly advantageous for drugs those are specifically absorbed from the stomach or the proximal part of the small intestine.⁵⁵ The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. It reduces the side effects which are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.
- **Absorption enhancement:** Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.⁵⁵
- **Minimize adverse activity at the colon:** Retention of the drug in the HBS systems 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 GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.
- **Reduce fluctuations of drug concentration:** Continuous input of the drug following controlled release gastro-retentive dosage form 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.

CONCLUSION

Drug absorption in the GIT is a highly variable procedure and prolonging GR of the dosage form extends the time for drug absorption. The FDDS become an additional

advantage for drugs that are absorbed primarily in the upper part of GI tract, i.e., the stomach, duodenum, and jejunum. Floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability controlled delivery of many drugs. FDDS promises to be a potential approach for gastric retention. Although there number of difficulties to be solved out to achieve prolonged gastric retention. In spite of its various limitations serious efforts are being done to commercialize this delivery system.

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