

Floating Drug Delivery Systems: A Review

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Abstract

In the recent years, scientific and technological advancements have been made in the research and development of novel drug delivery systems by overcoming physiological troubles such as short gastric residence times and unpredictable gastric emptying times. Several approaches are currently utilized in the prolongation of the gastric residence times, including floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices. This review explains briefly about formulation aspects, evaluation various floating drug delivery systems and application of these systems.

Keywords: Gastric residence time, Floating drug delivery system, Effervescent, Non-effervescent.

INTRODUCTION

The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, patient compliance and flexibility in formulation, etc. During the past few decades, numerous oral drug delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a specific period of time at a predetermined and controlled rate ^[1]. It is evident from the recent scientific and patent literatures that an increased interest in novel oral controlled release dosage forms that designed to be retained in the gastrointestinal tract (GIT) for a prolonged and predictable period of time exists today ^[2]. Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS) ^[3], low-density systems ^[4], raft systems incorporating alginate gels ^[5], bioadhesive or mucoadhesive systems ^[6], high-density systems ^[7], superporous hydrogels ^[8] and magnetic systems ^[9]. The current review addresses briefly about the FDDS that is one of the most leading methodologies in gastroretentive drug formulations.

Floating drug Delivery System

Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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. 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. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. Table 1 enlists examples of various drugs formulated as different forms of FDDS.

Drug Candidates Suitable for FDDS

- Drugs that have narrow absorption window in GIT (e.g. L-DOPA, p-aminobenzoic acid, furosemide, riboflavin) ^[2]
- Drugs those are locally active in the stomach (e.g. misoprostol, antacids) ^[10]
- Drugs those are unstable in the intestinal or colonic environment (e.g. captopril, ranitidine HCl, metronidazole) ^[11]
- Drugs that disturb normal colonic microbes (e.g. antibiotics used for the eradication of *Helicobacter pylori*, such as tetracycline, clarithromycin, amoxicillin) ^[12]
- Drugs that exhibit low solubility at high pH values (e.g. diazepam, chlordiazepoxide, verapamil) ^[13]

Table 1 - List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems

Dosage Form	Drugs
Tablets	Cholrpheniramine maleate, Theophylline, Furosemide, Ciprofloxacin, Captopril, Acetylsalicylic acid, Nimodipine, Amoxycillin trihydrate, Verapamil HCl, Isosorbide di nitrate, Isosorbide mononitrate, Acetaminophen, Ampicillin, Cinnarazine, Dilitiazem, Florouracil, Prednisolone,
Capsules	Nicardipine, Chlordiazepoxide HCl, Furosemide, Misoprostal, Diazepam, Propranolol, Urodeoxycholic acid.
Microspheres	Aspirin, Griseofulvin, and p-nitroanilline, Ketoprofen, Iboprufen, Terfenadine.
Granules	Indomethacin, Diclofenac sodium, Prednisolone
Films	Cinnarizine

Advantages of FDDS ^[14, 15]

1. The Floating systems are advantageous for drugs meant for local action in the stomach. E.g. antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
3. The Floating systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
4. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents.
5. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

Disadvantages of FDDS

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM

- a. **Density:** Density of the dosage form should be less than the gastric contents (1.004gm/ml).
- b. **Size and Shape:** Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT for 90 to 100 % retention at 24 hours compared with other shapes. ^[16]
- c. **Fed or Unfed State:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours. 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. ^[17]
- d. **Nature of the meal:** Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release. ^[18]
- e. **Caloric Content:** GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

- f. **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.^[19]
- g. **Gender:** Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
- h. **Age**^[20]: Elderly people, especially those over 70 years have a significantly longer GRT.^[21]
- i. **Posture**^[20]: GRT can vary between supine and upright ambulatory states of the patients
- j. **Concomitant drug administration:** Anticholinergic like atropine and propenthelin opiates like codeine and prokinetic agents like metoclopramide and cisapride.

TYPES OF FLOATING DRUG DELIVERY SYSTEMS

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS.

i) Non-Effervescent FDDS^[19, 22]

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carboxypol.

The various types of this system are as:

a. Single Layer Floating Tablets: They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

b. Bi-layer Floating Tablets: A bi-layer tablet contain two layer one immediate release layer which releases initial dose

from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach

c. Alginate Beads: Multi-unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

d. Hollow Microspheres: Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40 °C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.

ii) Effervescent FDDS

a. Volatile liquid containing system: The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Poly vinyl alcohol, Polyethylene, etc. that gradually dissolves 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.^[23]

Table 2 - Marketed Products of FDDS

Dosage Form	Drugs	Brand Name	Company, Country
Floating Controlled Release Capsule	Levodopa, Benserazide	MODAPAR	Roche Products,USA
Floating Capsule	Diazepam	VALRELEASE	Hoffmann-LaRoche,USA
Effervescent Floating Liquid alginate Preparation	Aluminium hydroxide, Magnesium carbonate	LIQUID GAVISON	Glaxo Smith Kline,INDIA
Floating Liquid alginate Preparation	Aluminium - Magnesium antacid	TOPALKAN	Pierre Fabre Drug,FRANCE
Colloidal gel forming FDDS	Ferrous sulphate	CONVIRON	Ranbaxy,INDIA
Gas-generating floating Tablets	Ciprofloxacin	CIFRAN OD	Ranbaxy,INDIA
Bilayer floating Capsule	Misoprostal	CYTOTEC	Pharmacia,USA

b. *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. ^[23, 24] Some FDDS products available in the market are listed in Table 2.

FORMULATION OF FLOATING DOSAGE FORM

The following types of the ingredients can be incorporated in to FDDS ^[21]

- Hydrocolloids
- Inert fatty materials
- Release rate accelerants
- Release rate retardant
- Buoyancy increasing agents
- Miscellaneous

Hydrocolloids: Suitable hydrocolloids are synthetics, anionic or non ionic like hydrophilic gumes, modified cellulose derivatives. Eg. Accasia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2. Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system,

it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy.

Inert fatty materials: Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increases the buoyancy. Eg. Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and mineral oils can be used.

Release rate accelerant: The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5-60% by weight.

Release rate retardant: Insoluble substances such as dicalcium phosphate, talc, magnesium strearete decresed the solubility and hence retard the release of medicaments.

Buoyancy increasing agents: Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80 % by weight.

Miscellaneous: Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporates in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems.

EVALUATION OF FLOATING DOSAGE FORMS

A. For Single Unit Dosage Forms ^[25] (Eg: tablets)

(i) Floating lag time: It is the time taken by the tablet to emerge onto the surface of dissolution medium and is expressed in seconds or minutes.

(ii) In vitro drug release and duration of floating: This is determined by using USP II apparatus (paddle) stirring at a speed of 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 analysed 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.

(iii) In vivo evaluation for gastro-retention: This is carried out by means of X-ray or Gamma scintigraphic monitoring of the dosage form transition in the GIT. The tablets are also evaluated for hardness, weight variation, etc.

B. For Multiple Unit Dosage Forms ^[26] (Eg: 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:

(i) Morphological and dimensional analysis with the aid of scanning electron microscopy (SEM). The size can also be measured using an optical microscope.

(ii) % yield of microspheres: This is calculated from

$$\frac{\text{Weight of microspheres obtained}}{\text{Total weight of drug and polymer}} \times 100$$

(iii) Entrapment efficiency: The drug is extracted by a suitable method, analysed and is calculated from

$$\frac{\text{Practical amount of drug present}}{\text{Theoretical drug content}} \times 100$$

(iv) 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.

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

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

(v) Drug-excipient (DE) interactions: This is done using FTIR. Appearance of a new peak, and/or disappearance of original drug or excipient peak indicates the DE 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.

APPLICATION OF FLOATING DRUG DELIVERY SYSTEM

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 follow:

i) Sustained Drug Delivery: FDSDS 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.

Eg. Sustained release floating capsules of nifedipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).^[27]

ii) 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.

Eg. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. Area under Curve obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets. ^[28] **iii)**

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.

Eg. 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%). ^[28]

CONCLUSION

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the gastrointestinal tract is to control the gastric residence time using gastroretentive dosage forms that will provide us with new and important therapeutic options. Floating drug delivery system can provide sufficient gastric retention which may help to provide sustained release dosage form with enhanced absorption. Number of commercial product and patent issued in this field are evident of it.

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