Review Article

Review on Floating Drug Delivery System

Pradip. S. Patil*, Hitesh A. Patil, SA. Tadavi and SP. Pawar

P.S.G.V.P.M's. College of Pharmacy, Shahada - 425409,

Tal & Dist – Nandurbar, Maharashtra, India.

ABSTRACT

Gastric emptying is a complex process and makes in-vivo performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the gastric retention time of the drug-delivery systems for more than 12 hours. Floating drug delivery systems release gas (CO_2), thus reduce the density of the system and remain buoyant in the stomach for a prolonged period of time and released the drug slowly at a desired rate so it can be used to prolong the gastric residence time in order to improve the bioavailability of drug. The recent developments of FDDS including the physiological and Formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail.

Keywords: FDDS, prolonged period, Bioavailability, gastric retention time etc.

INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems.[1] Floating systems 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.[2] 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. Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation. 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.

Classification of Floating Drug Delivery System

(A) Non-effervescent systems: This type of system, after swallowing, swells via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. The formulation methods of such type dosage forms involves the mixing of the drug with a gel, which swells when comes in contact with gastric fluid and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer provides buoyancy these dosage forms. The most commonly used excipients in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, carbopol agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into four sub-type [3,4,5]

(i) Colloidal gel barriersystem: These types of systems contain drug with gel-forming hydrocolloids which allow them to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug at its

absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid as hydroxypropyl cellulose, hydroxyethyl cellulose. This hydrocolloid hydrates and forms a colloid gel barrier around its surface after coming in contact with gastric fluid and also helps in sustain releasing of drug

(ii) Microporous Compartment system: In this technology, a drug reservoir is encapsulated inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed. This sealing prevents any direct contact of gastric surface with the un-dissolved drug. The flotation chamber containing the delivery system to float over the gastric content entrapped air allows, in the stomach. Gastric fluid enters through an aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

(iii) Alginate beads: To develop Multi-unit floating dosage forms, the freeze dried calcium alginate has been used. Spherical beads of approximately 2.5 mm in diameter can be prepared by the precipitation of calcium alginate via dropping sodium alginate solution into aqueous solution of calcium chloride. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, it leads to the formation of a porous system which can maintain a floating force for over 12 hours. These floating beads prolonged residence time for more than 5.5 hours.

(iv) Hollow Microspheres/Microballons: A novel emulsion solvent diffusion method used to prepare hollow microspheres loaded with drug in their outer polymer shelf 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 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed in the internal cavity of microsphere of the polymer and drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12h.

(B) Effervescent Systems: These buoyant systems utilize matrices prepared with swellable polymers such as methocel polysaccharides (e.g., chitosan) and effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that when it arrives in the stomach carbon dioxide is released, causing the formulation to float in the stomach [6.]

Mechanism of floating systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so 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 (Fig.: 1) 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. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object.

The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra-gastric buoyancy capability variations [7].

$$F = F_{buoyancy} - F_{gravity} = (Df - Ds)\, gV$$

Where, F= total vertical force, Df = fluid density, Ds = object density, V = volume and g = acceleration due to gravity.

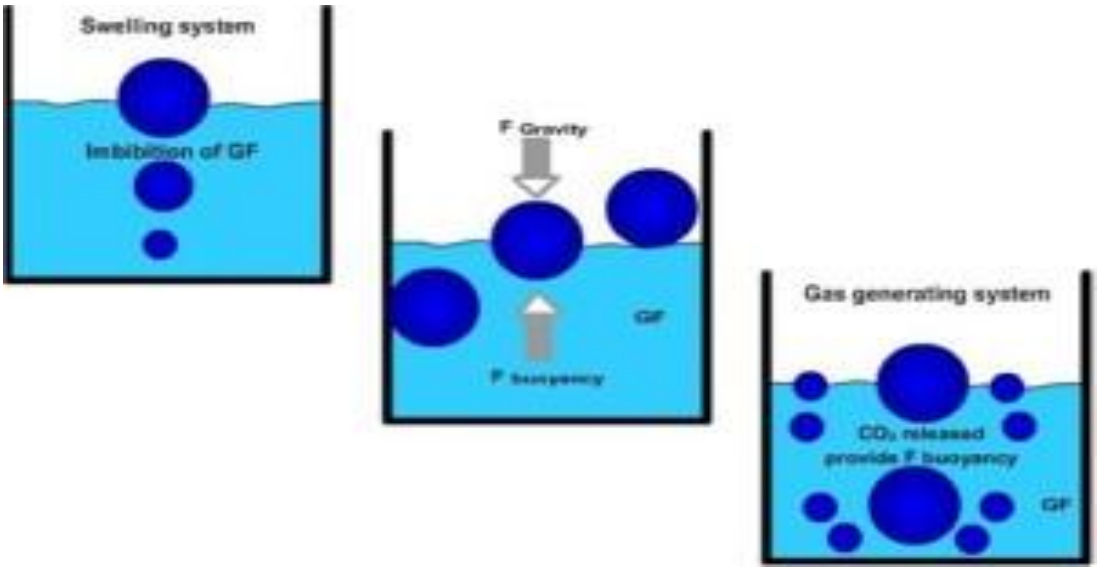

Fig.1: Mechanism of Floating Drug Delivery system

ADVANTAGES OF FDDS

1. Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
2. FDDS are advantageous for drugs meant for local action in the stomach e.g.: Antacids
3. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach to get a relatively better response.
4. Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
5. The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids.
6. Drugs with considerably short half-life can be administered in this manner to get an appreciable therapeutic activity.
7. Enhancement of the bioavailability for drugs which can metabolized in the upper GIT.[8,9.]

DISADVANTAGES OF FDDS

1. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
2. Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
3. One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.
4. These systems also require the presence of food to delay their gastric emptying.
5. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
6. High variability in gastric emptying time due to its all (or) non-emptying process.
7. Patients should not be dosed with floating forms just before going to bed[9,10,11].

Methods for Preparing Floating Dosage Form

Following approaches can be used for preparing floating dosage forms

1. Using gel-forming hydrocolloids such as hydrophilic gums, gelatin, alginates, cellulose derivatives, etc.
2. Using low-density enteric materials such as methacrylic polymer, cellulose acetate phthalate.
3. By reducing particle size and filling it in a capsule.

4. By forming carbon dioxide gas and subsequent entrapment of it in the gel network.
5. By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.
6. By incorporation of inflatable chamber, which contained in a liquid e.g. solvent that gasifies at body temperature to cause the chambers to inflate in the stomach.

EVALUATION PARAMETERS

1. **Size and Shape Evaluation:** The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability**.** The particle size of the formulation was determined using Sieve analysis (Jayant, Mumbai), Air elutriation (Bahco TM) analysis, Photo analysis, Optical microscope (Olympus, India, Pvt. Ltd), Electro résistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air Pollution Emissions Measurements etc.
2. **Floating Properties:** Effect of formulation variables on the floating properties of gastric floating drug delivery system was determined by using continuous floating monitoring system and statistical experimental design.
3. **Surface Topography:** The surface topography and structures were determined using scanning electron microscope (SEM, JEOL JSM – 6701 F, Japan) operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic Force Microscopy (AFM), Contact profilio-meter.
4. **Swelling Studies:** Swelling studies were performed to calculate molecular parameters of swollen polymers**.** Swelling studies was determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include ^{1}HNMR imaging, Confocal laser scanning micro- and fats scopy (CLSM), Cryogenic Scanning Electron Microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus (USP dissolution apparatus (usp-24) Lab-India Disso 2000) was calculated as per the following formula.

   Swelling ratio = Weight of wet formulation **/** Weight of formulations
5. **Determination of the Drug Content:** Percentage drug content provides how much amount of the drug that was present in the formulation. It should not exceed the limits acquired by the standard monographs. Drug content was determined by using HPLC, HPTLC methods, near infrared spectroscopy (NIRS), Micro-titrimetric methods, Inductively Coupled Plasma Atomic Emission Spectrometer (ICPAES) and also by using spectroscopy techniques (Elico. Limited, Hyderabad).
6. **Percentage Entrapment Efficiency:** Percentage entrapment efficiency was reliable for quantifying the phase distribution of drug in the pre-pared formulations. Entrapment efficiency was deter-mined by using three methods such as Micro dialysis method, Ultra centrifugation, and pressure Ultra filtration.
7. ***In-vitro* Release Studies:** *In vitro* release studies were performed to provide the amount of the drug that is released at a definite time period.
8. **Fourier Transforms Infrared Analysis:** Fourier transform infrared spectroscopy (FTIR, Shimadzu, Model-RT-IR-) is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. FourierTransform Infrared Analysis (FTIR) measurements of pure drug, polymer and drug-loaded polymer formulations were obtained on FTIR. The pellets were prepared on KBr-press under hydraulic pressure of 150 kg/cm^{2}; the spectra were scanned over the wave number range of 3600 to 400 cm^{-1} at the ambient temperature.
9. **Differential Scanning Calorimetry (DSC):** are generally used to characterize water of hydration of pharmaceuticals. Thermo-grams of formulated preparations were obtained using DSC instrument equipped with an intercooler. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermitically sealed in an aluminum pan and heated at a constant rate of 10°C/min; over a temperature range of 25° C – 65°C.Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50 ml/min [12,13,14]

FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS:- There are several factors that can affect gastric emptying of an oral dosage form which include density,

size and shape of dosage form, feeding state, biological factors such as age, gender, posture, body mass index, disease state etc.[15]

1) Effect of Dosage Form Size & Shape

Small size tablets are emptied from the stomach during the digestive phase while large size units are expelled during the house keeping waves found that floating unit with a diameter equal or less than 7.5 mm had larger gastric residence time (GRT) compared to non-floating units but the GRT was similar for floating and non-floating units having a large diameter of 9.9 mm. They found that GRT of non-floating units were much more variable and highly dependent on their size which are in the order of small < medium < large units. Moreover, in supine subjects, size influences GRT of floating and non- floating form. Tetrahedron and ring shaped devices have a better GRT as compared with other shapes.

2) Gender, Posture & Age

Mean ambulatory GRT in males (3.4±0.6 hour) is less compared with their age and race-matched female counterparts (4.6±1.2 hour) regardless of their weight, height and body surface. Women emptied their stomach at a lower rate than men even when hormonal changes due to menstrual cycle were minimized. The mean GRT in the supine state (3.4±0.8 hour) was not statically significant from that in the upright, ambulatory state (3.5±0.7 hour). In case of elderly, the GRT was prolonged especially in subject more than 70 years old (mean GRT – 5.8 hour).

3) Effect of Food & Specific Gravity

To float FDDS in the stomach, the density of dosage form should be less than gastric content i.e.1.0 g/cm^3. Since, the bulk density of a dosage form is not a sole measure to describe its buoyant capabilities because the magnitude of floating strength may vary as a function of time and gradually decrease after immersing dosage form into fluid as a result of development of its hydrodynamic equilibrium. Various studies have shown the intake of food as main determinant of gastric emptying rather than food. Presence of food is the most important factor effecting GRT than buoyancy. GRT is significantly increased under fed condition since onset of MMC is delayed. Studies show that GRT for both floating and non-floating single unit are shorter in fasted subjects (less than 2 hour), but significantly prolonged after a meal (around 4 hour).

4) Nature of Meal & Frequency of Food

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to fed state, to increase gastric emptying rate and prolonging the drug release. Diet rich in protein and fat can increase GRT by 4-10 hours.

5) Type of Formulation

Multiple unit formulation show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profile or containing incompatible substances and permit a large margin of safety against dosage form failure compared with single unit dosage form.

S. No.	Dosage Forms	Drugs
1.	Floating microspheres	Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen[16], Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol , Tranilast.[17,18]
2.	Floating granules	Diclofenac. sodium, Indomethacin and Prednisolone.
3.	Films	Cinnarizine, Albendazole.
4.	Floating tablets and Pills	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate, Para- aminobenzoic acid, Piretanide Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol, pentoxyfilline and Diltiazem HCl.[19,20,21]
5.	Floating Capsules	Chlordiazepoxide hydrogen chloride, Diazepam Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin, and Propranolol.[22,23]

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS

1) Enhanced Bioavailability

The bioavailability of riboflavin 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.

2) 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. These systems are relatively larger in size and passing from the pyloric opening is prohibited.

3) **Site-Specific Drug Delivery Systems**

These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the high conc^{n} of drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency. E.g.: Furosemide and Riboflavin.

4) 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.

5) **Minimized 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 betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon
leads to the development of microorganism's resistance.

6) **Reduced Fluctuations of Drug Concentration**

Continuous input of the drug following CRGRDF 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

The floating drug delivery system was prepared to increase the gastric retention time of the dosage form and to control drug release. 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 gastro-retentive dosage forms that will provide us with new and important therapeutic options. Floating matrix tablets are designed to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

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