



A review on floating drug delivery systems

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ABSTRACT

Currently, several approaches have been utilized in the extension of gastric residence time which includes FDDS, swelling and expanding systems, bio-adhesive systems, modified shape systems and high density systems. Among the gastro retentive dosage forms, floating dosage forms are coming out as a predicting dosage forms. Floating drug delivery systems (FDDS) have bulk density less than the gastric fluid contents and so, rest float on the stomach contents for a sustained period of time and ejecting the drug slowly at a desired rate from the system and enhance the bio-availability of the drug having narrow absorption window. Various components like hydrocolloids, inert fatty materials and buoyancy increasing agents can be used to formulate floating dosage forms. Various categories like antacids, anti-diabetic, anti-fungal and anticancer drugs are formulated into FDDS. The present review article addresses briefly about the back ground, advantages, disadvantages applications, approaches, and future aspects of floating drug delivery systems. This review also emphasizes about characterization parameters such as FT-IR, DSC, X-RD and evaluation parameters like floating time, drug release and swelling studies are also discussed.

Keywords: Buoyancy; Gastro Retentive System; Hydrodynamically Balanced System; Swelling Index; Absorption Window; Crushing Strength; Friability

INTRODUCTION

Oral route is considered as most natural and unpredictable route due to its relief of administration, improved patient compliance and most widely utilized route of administration (Basak SC. *et al.*, 2004). But a major problem in oral controlled drug delivery is that not at all the drug candidates are absorbed uniformly throughout the gastro intestinal tract (GIT). Some medicaments are absorbed in a special segment of GIT, such drugs are said to have an absorption window. Thus the success of oral controlled drug delivery has faced some troubles related with short gastric residence time and unpredictable gastric emptying rate (Iannuccelli V. *et al.*, 1998). To extend and control gastric emptying time is different for dosage forms which is helpful to occupy in the stomach for a prolonged time than the conventional dosage form. One of such troubles is the ability to confine the dosage form in the desired area of GIT (Chein J. *et al.*, 2000). Therefore various approaches have been suggested to retain the dosage form in the stomach includes bio adhesive sys-

tems, floating systems, swelling and expanding systems and delayed gastric emptying systems. But the floating and bio adhesive systems are under research by the scientists (Singh B. *et al.*, 2000). The concept of FDDS was 1st in the literatures of 1968, when Daviis disclosed a method to defeat the problems experienced by some persons choking or gagging after swallowing medicinal pills. Then, he proposed that such problems could be overcome by providing pill having a density of < 1.0 gm/cm³, so that the pill will buoyant on water surface. Since then various approaches have been develop an ideal floating drug delivery system (Jagadeesh N. *et al.*, 2009). It is believed that the entire problems that are observed through oral controlled drug delivery can be overcome by FDDS which is interesting and present their own advantages (Garg R. *et al.*, 2008). In future, it is expected that they will be of enhancing importance and finally lead to improved efficiencies of pharmacotherapy.

Floating Drug Delivery Systems

Floating dosage form /hydro dynamically controlled systems are less density systems that are having enough buoyancy to float over the gastric content and stay buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The drug is released slowly at particular rate from the system, when it is floating on the gastric contents. The residual time is completed from stomach, after release of the drug. This results in an increased GRT and a bet-

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Received on: 29-09-2014

Revised on: 22-10-2014

Accepted on: 24-10-2014

ter control of the variations in plasma drug concentration (Mayavanshi AV. *et al.*, 2008). It is believed that to keep the dosage from reliably float on the surface of the meal besides a minimal gastric content is needed and also a minimal level of floating force is also required (Figure 1).

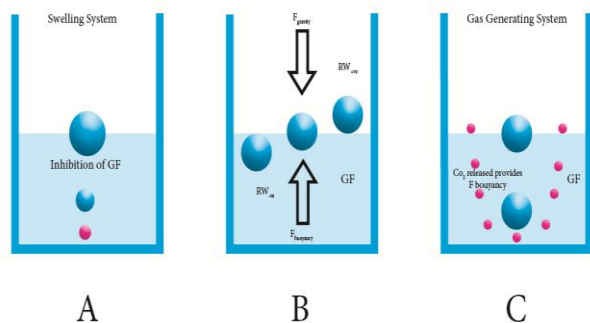


Figure 1: Mechanism of Floating Systems

Many floating systems have been developed based on the granules, powders, capsules, tablets, hollow microspheres, and laminated films.

Factors Affecting Floating Drug Delivery System

Meals

The rate of gastric emptying time depends upon the nature of meals (Arunachalam A. *et al.*, 2011) and caloric content of the meals.

Nature of meals

The fatty acids and salts can alter the gastric motility of the stomach to a fed state (Chein YW. *et al.*, 2004) thus decreasing gastric emptying rate and provide prolonged release.

Caloric content

The GRT can be increased by 4 to 10 hours with meals that are high in proteins and fats (Chungi VS. *et al.* 1979).

GI Fluid Content

The remaining volume of stomach is 25 to 50 ml. When the GI fluid volume is big (Sheth PR. *et al.*, 1984), the gastric emptying is faster. The GI fluids taken at body temperature leave the stomach faster than colder or warmer fluids.

Dosage form related factors

Density

The floating dosage form having a density (Gergogianis YS. *et al.*, 1993) $< 1.0 \text{ gm/cm}^3$ than that of the gastric fluid floats. On its way from the pyloric sphincter, the unit dosage form is retained in the stomach for prolonged period.

Size of dosage form

The unit dosage form containing $> 7.5\text{mm}$ are reported to have an increase GRT compared with diameter of

9.9 mm. Small tablets get out from the stomach during the digestive phase while the large sized tablets are discharged during the housekeeping waves.

Shape of Dosage Form

The dosage (Garg R. *et al.*, 2008) form having a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) was reported to have improve GIT for 90 to 100% retention and more suitable for FDDS as compared with other shapes.

Polymer Viscosity Grade

Floating properties and drug release are affected by the viscosity of polymer and their interaction with low viscosity polymer (HPMC K100 LV) is more good than high viscosity polymer (HPMC K4M) in increasing the floating properties.

Fed condition

Fed or unfed state

In fasting condition, the GI motility is characterized by periods of strong activity of the migrating myoelectric complex (MMC) which occurs every 1.5 to 2 hr. However, in the fed state, the GRT is considerably longer and MMC is delayed.

Frequency of feed

GRT increases by 400 minutes when a multiple meals are given compared with a single meal due to the frequency of MMC.

Patient related factors

Gender

Women have slower gastric emptying time when compared to men. Ambulatory GRT in meals ($3.5 \pm 0.4\text{hr}$) is less compared with their age and race. Counterparts ($4.6 \pm 1.2\text{hr}$) regardless of the height, weight and body surface (Mojaverian P. *et al.*, 1988).

Age

In elderly (Patel GM. *et al.*, 2007) group Gastric Emptying Time is lower when compared to Youngers. Inter and intra-subject variation is also observed in gastric and intestinal transit time. Especially those over 70 years have a significantly longer Gastric Emptying Time.

Posture

Gastric retention time varies in between bend position and upright position in patient.

Concomitant intake of drug

Some drugs like anti cholinergic (Atropine), Opiates (codeine), Prokinetic agents (metoclopramid) affect the performance of FDDS. The GI motility of drugs decreases so, that can increase gastric emptying time (Chawla G. *et al.*, 2003).

Biological factors: Diabetes and Crohn's disease etc.

Advantages of floating drug delivery systems

- FDDS are advantageous (Babu VBM. *et al.*, 1990) for drug candidates that are meant for local action within the stomach. E.g. Antacids.
- Acidic substances (Hetal N. *et al.*, 2000) like Aspirin can cause irritation on the stomach wall when comes in contact with it. So, floating dosage form may be helpful for the administration of Aspirin and similar drug candidates.
- Floating dosage forms may be beneficial in case of vigorous intestinal movement and certain types of Diarrhoea to keep the drug in buoyant condition in the stomach to get a improve response (Sanjay Garg. *et al.*, 2003).
- Floating dosage forms (Yie W. *et al.*, 1992) are beneficial for drugs that are absorbed through the stomach. E.g. Ferrous salts and Antacids.
- It is expected that a drug will be completely absorbed from floating dosage forms. It stays in the solution even at the alkaline pH of the intestine (Vedhahari B.N, *et al.*, 2010).

Disadvantages

- Floating system is not desirable for those drugs that are having solubility problems in Gastro retention time fluids.
- One of the demerits of FDDS, it requires a sufficient higher level of gastric fluid for drug delivery to float in the stomach (Shweta Arora. *et al.*, 2005).
- The medicaments which are going to be absorbed through the GIT and which undergoes fast disintegration as FDDS. E.g. Nifedipine.
- Floating drug delivery systems also require the presence of food to delay the gastric emptying (Gangadharappa HV. *et al.*, 2007).

Limitations of Floating Drug Delivery Systems

- Drugs which have solubility and stability troubles in GIT are not desirable candidates for these types of systems.
- A high level of fluid in the stomach is wanted for drug delivery to float and work efficiently.
- Dosage forms which are irritant to Gastric mucosa are also not desirable.
- Drug's such as a Nifedipine, which undergoes first pass metabolism, is not desirable for the preparation of these types of systems.
- The dose substances that are unstable in acidic environment of the stomach are not desirable candidates to be incorporated in the systems (Talwar N. *et al.*, 2001).

Classification of Floating Drug Delivery System

The Classification of floating drug delivery systems mainly classified into 2 types.

Non-effervescent systems

Colloidal gel barriers system

Micro porous compartment system

Alginate beads

Hollow microspheres/micro balloons

Effervescent systems

Volatile liquid containing systems

Gas-generating systems

Non-effervescent systems

Colloidal gel barriers system

Floating drug delivery system was first designed by sheath and Tossounian in 1975. Such system is composed of drug in gel-forming hydrocolloids meant to stay float on the gastric contents. This system is longer the gastric residence time and increased the conversion of drug into solution from which is ready for absorption. These systems can incorporate a higher level of gel-forming (20-75%), highly swelling, hydrocolloids of cellulose (Eg. HPMC, HEC, HPC, and NaCMC), polysaccharides and matrix forming polymers such as Polyacrylates, Polycarbophil and Polystyrene, which are incorporated into either tablets or capsules when the system comes in contact with gastric fluid, the hydrocolloids in the system will hydrate and form a colloidal gel barrier around the surface of its. The rate of fluid penetration into the device and release of drug can be controlled by the gel barrier.

The exterior surface of dosage form comes in contact with the GI fluid, the hydrocolloid layer is going to hydrate. The swollen polymer maintains a density less than a unit and gives a property of floating to their dosage forms (Mathur P. *et al.*, 2001). A bi-layered tablets preparations which contain one quick release layer and one sustained release layer. Such quick release layer releases the initial dose and sustained release layer absorbs GI fluids surface. This results in a system with bulk density less than the gastric fluid, and it allows to stay float in the stomach contents for an extended period of time.

Micro porous compartment system

A drug reservoir is encapsulated inside a micro porous compartment which is having pores throughout its top and bottom walls to prevent any direct contact of the drug with gastric mucosal surface (Harrigan RM. *et al.*, 1977). The upper walls of the drug reservoir compartment are completely sealed. This system is having a floatation chamber which is filled with air and it allows the delivery system to float over the gastric fluid contents. When the system comes in contact with the

electrons in gastric content, the GI fluid enters into the pores, dissolving the drug and carries the drug for uninterrupted transport across the intestine for absorption (Jain NK. *et al.*, 2004).

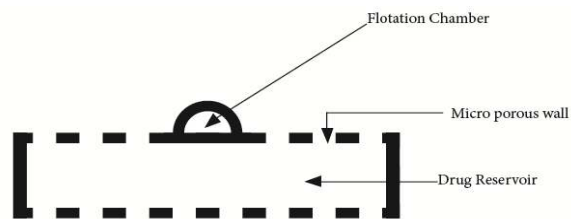


Figure 2: Microporous Compartment System

Alginate beads

The freeze dried calcium alginate has been used to develop the multiple-unit dosage form. By the dropping sodium alginate solution into the aqueous solution of calcium chloride, solution form the calcium alginate is going to be precipitated. (Whiteland L. *et al.*, 1996) By this procedure, ball-shaped beads of approximately 2.5 mm in diameter can be prepared. The resulting spherical beads are separated, then snapfrozen in liquid N₂ and finally freeze dried at 40°C for 24hrs. This leads to the formation of a porous system, which can maintain a floating force for over 12hr. These floating alginate beads prolongs the gastric residence time for more than 5.5 hr. than solid beads.

Micro balloons/ Hollow microsphere

To prepare these systems are emulsion solvent diffusion method was used. The dichloromethane or ethanol solution of the drug and an enteric polymer was poured into an agitated solution of polyvinyl alcohol (PVA) which was temperature controlled at 40°C.

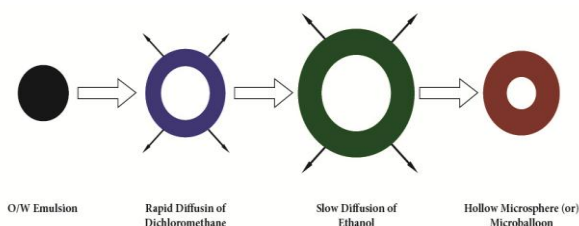


Figure 3: Hollow microspheres

The gas phase is seen in the dispersed polymer due to the evaporation of dichloromethane. The *in-vitro* experiments revealed that the microballoons floated on over the surface of the acidic dissolution containing surfactant for more than 12hr (Kawashima Y. *et al.*, 1992).

Effervescent Systems

Volatile liquid containing system

By incorporating an inflatable chamber which is having a liquid used ether or cyclopentane, the drug delivery system can be sustained drug released. It is observed that liquid converts to gas body temperature and the inflation causing in the chamber in stomach. The volatile liquid containing system having two chambers

which are classified by an impermeable, pressure-responsive and movable bladder. The 1st chamber contains volatile liquid, the device inflates and the drug is continuously released from drug reservoir into the gastric fluid. The device may also consist of a bio compatible plug made up of Polyethylene or PVA, that gradually dissolves and causes the inflatable chamber release gas and after a predetermined time it is going to collapse to permit the spontaneous evacuation of the inflatable system from stomach (Jain NK. *et al.*, 2004).

Gas-generating system

Gas-generating system are utilize an effervescent reaction between the carbonate/bicarbonate salts and citric/tartaric acid to liberate CO₂, which is entrapped in the gelled hydrocolloid layer of the system and thus result in a reduction of specific gravity and making it buoyant over gastric contents. The system may be either single layered where the CO₂ generating components are directly mixed with the tablet matrix or bilayered, where the gas generating components are compressed in one layer and the drug in another layer which are formulated for a sustained release. The ratio of 0.76:1 is the optimum ration of citric acid and NaCO₃ for gas generation (Patil JM. *et al.*, 2011).

The common approach used for this gas generation system includes the beads loaded with bicarbonate and coating with the ethyl cellulose. The coating is insoluble but it permits water. When water enters into the system, CO₂ is released, causing the beads to buoyant over the gastric contents. Other reported approach includes multiple unit floating pills and floating systems based on ion-exchange resin technology etc. (Chawla G. *et al.*, 2003).

Approaches to design FDSS

To improve the GRT of the dosage form, among the various approaches that have been design. Single unit and multiple unit dosage forms are the two approaches which are used to design the floating dosage forms (Punitha K. *et al.*, 2011).

Single unit dosage forms

The polymers like HPC, HPMC, SCMC and ethyl cellulose are extensively used in the floating dosage forms. To control the drug release, a self-correcting floatable asymmetric configuration of drug delivery system is employed with disproportionate 3-layer matrix technology. Main problem with the single-unit dosage form is, it includes a permanent retention of rigid long-sized single unit form especially in patients with intestinal adhesion, bowel obstruction, gastropathy or a narrow pyloric opening (normal diameter of pyloric sphincter is 12.8±7.0mm). The dosage forms are not be given to a patient just before going to the bed because the gastric emptying of such dosage forms occurs fast when the subject is in supine posture. (Soppimath KS. *et al.*, 2001).

Multiple-Unit Dosage Forms

The designing of multiple-unit dosage form is to formulate a reliable formulation that has the advantages of the single-unit form and also is devoid of the above mentioned weaknesses of single-unit formulations (Soppimath KS. *et al.*, 2011). In pursuit of this endeavor many multiple unit floatable dosage forms have been designed. Microspheres having high loading capacity and many polymers have been such as albumin, starch, gelatin, polymethacrylate, polyacrylamine and polyalkylcyanoacrylate. Ball-shaped polymeric microspheres have been prepared. Microspheres have a characteristic internal hollow structure and show excellent *in-vitro* floatability. In CO₂ generating multiple unit oral dosage forms, several devices with features that extend, unfold are inflated by carbon dioxide generated in the devices after administration. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~ 12 to 18 mm in their expanded state is exceeded (Ichikawa M. *et al.*, 1991).

Raft forming system

The mechanism involved in the formation include formation of viscous cohesive gel which contacts with GI fluids, where in each portion of the liquid swells forming a continuous layer called a Raft (Kawashima Y. *et al.*, 1992). The raft buoyancy created to CO₂ and it the formation and act as a barrier to prevent the reflux of gastric contents like enzymes and HCl in the esophagus. The raft system canting a gel forming agent and alkaline bicarbonates or carbonates responsible for formulation of the less dense system and float on the gastric fluids.

Applications of floating drug delivery systems

Sustained Drug Delivery

Hydrodynamically balanced system can remain in the stomach for prolong periods and hence drug can release prolonged period of time. The trouble of short GRT encountered with an oral controlled release formulation overcome with these systems (Ritschel W. *et al.*, 2001). The systems containing bulk density of < 1 result that which they can float on the gastric fluid. Recently sustained release floating capsules of Nifedipine hydrochloride were developed and were evaluated *in-vivo*.

Site-Specific Drug Delivery

- These systems are beneficial for drugs that are specifically absorbed in stomach or the proximal part of the small intestine. E.g. Riboflavin and Furazolidone.
- The monolithic floating dosage form with longer gastric residence time was developed and the bioavailability was increased. AUC of the floating tablets was approximately 1.8 times more than those of conventional tablets.

- Bilayer-floating capsule was formulated for local delivery of Misoprostol, which is a synthetic analogue of prostaglandin E1 used as a protectant of gastric ulcers caused by taking of NSAIDs. By targeting slow delivery of the stomach, desired therapeutic levels could be achieved and drug waste could be reduced.

Absorption Enhancement

Medicaments which 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.

Table 1: Gastro retentive dosage forms available in Market

Brand name	API	Dosage form
Cifran OD	Ciprofloxacin (1g)	Gas generating Floating Form
Gabapentin GR	Gabapentin (In Phase-III clinical trials) Accordion Pill TM	Polymer Based
Glumetza	Metformin	Polymer Based
proQuin XR	Ciprofloxacin	Polymer Based
Coreg CR(Carvedilol)	Carvedilol	Gastro retention with osmotic system
Baclofen GRS	Baclofen	Coated multi-layer floating & swelling system
Madopar	Levodopa and Benzerzide	Floating, CR Capsule
Valrelease	Diazepam	Floating Capsule
Cytotec	Misoprostol (100mcg/200mcg)	Bilayer Floating Capsule
Liquid Gaviscon	Alginic acid and sodium bicarbonate	Effervescent floating liquid alginate preparation
Topalkan	Aluminium magnesium antacid	Floating Liquid Alginate
Convion	Ferrous Sulphate	Colloidal gel forming FDDS

Characterization and Evaluation for FDDS

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry is (Girish S. *et al.*, 2007) used to characterize of hydration in pharmaceuticals. Thermo grams of formulated dosage obtained using DSC instrument equipped with an intercooler. It was used to calibrate Indium/Zinc standards, temperature and enthalpy scale, preparations were hermitically

sealed in an aluminium pan and heated at 10°C/min at constant rate, with a temperature range of 25°C – 65°C. Inert atmosphere was maintained by nitrogen gas at a flow rate of 50ml/min.

Fourier Transform Infrared Analysis

FT-IR is used to identify inorganic, polymeric, and some organic materials as well as for functional group determination. The FT-IR measurements of pure drug, polymer and drug loaded polymer formulations were obtained on FT-IR. The pellets were prepared on KBr-press under a hydraulic pressure of 150kg/cm². The spectra were scanned over the wave number range of 3600 to 400cm⁻¹ at the ambient temperature.

Powder X-ray diffraction

Study is used for the study of polycrystalline materials and eminently fitted for the routine characterization of pharmaceutical solids (Oth M. *et al.*, 1992). Samples were irradiated with radiation and analysed between the 2°C and 60°C. The voltage and current used were 30KV and 30mA respectively.

Size and Shape Evaluation

The formulation particle size, shape, solubility rate is determined by using Air elutriation analysis, Sieve analysis, Optical microscope, Photo analysis, Electro resistance counting methods (Coulter counter), Sedimentation techniques, Ultrasound Attenuation Spectroscopy, Laser diffraction methods and Air Pollution Emissions Measurements etc.

CONCLUSION

Absorption of dosage form in the GIT is the procedure which depends upon gastric emptying and other factors. Floating drug delivery system is promises to be a potential approach for gastric retention time. Designing GRDDS needs a thorough understanding of the physicochemical properties of the drug, the physiological factors of the GIT and formulation strategies. A critical consideration of the key role of these factors can help in designing of device like GRDDS. To formulate an efficient FDD System is a challenge and the work will extend, until an ideal approach with future applicability and feasibility arrives although there are number of difficulties in designing of prolonged gastric retention system, a GRDDS systems are focusing towards to commercialize this technique in future.

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