

Review: An Overview on Gastroretentive Floating Tablet

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ABSTRACT

Gastroretentive dosage forms (GRDF) has received significant interest in the past few decades as they can improve the limitation of most conventional and oral controlled release drug delivery system related to fast gastric-emptying time. An optimum GRDF system can be defined as a system which retains in the stomach for a sufficient time interval against all the physiological barriers, releases active moiety in a controlled manner. The developments of floating drug delivery system (FDDS) are achievement of these advanced technologies. In this drug is released from swollen matrix. These forms are expected to remain buoyant on gastric content without affecting intrinsic rate of emptying. This results in prolonged gastric

retention time of floating forms which improve bioavailability of drug and also improve clinical situations. The present review also reveals the recent development of FDDS including types, approaches for designing the floating dosage forms, their formulation aspects, advantages & disadvantages and evaluation of FDDS.

Keyword: Gastroretentive Dosage Forms, Gastrointestinal Tract, Bioadhesive Systems, Unfolding Systems, Density Controlled Systems.

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 etc¹. So the design of oral control drug delivery systems (ODDS) should be primarily aimed to achieve more predictable and increased bioavailability². 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 dose³⁻⁴. 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 absorbed⁵.

Gastroretentive drug delivery is an approach to prolong gastric residence time because these dosage forms can remain in the gastric region for long periods, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Over the

last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained at the bottom of the stomach⁶, low density (floating) systems that causes buoyancy in gastric fluid⁷⁻⁹, mucoadhesive systems that causes bioadhesion to stomach mucosa¹⁰, superporous hydrogel systems¹¹, unfoldable, extendible or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach^{12,13}, magnetic systems¹⁴ etc.

FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery systems (FDDS) are those systems which have a bulk density less than gastric fluids and because of this, these systems remains buoyant (3-4 hours) for a prolonged period of time in the stomach without affecting the gastric emptying rate. The drug is released slowly at the desired rate from the system and after release of the drug; the residual system is emptied from the stomach. As a result GRT is increased and fluctuations in plasma drug concentration can be better controlled¹⁵.

MECHANISM OF FLOATING SYSTEMS

While the system is floating on the gastric content the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. 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 side¹⁶. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

$$F = F \text{ buoyancy} - F \text{ gravity} = (Df - Ds) gv$$

Where, F= total vertical force, Df = fluid density, Ds = object density, v = volume and g = acceleration.

ADVANTAGES OF FDDS

Sustained drug delivery

Floating drug dosage forms can remain in the stomach for a long time and enhance the GRT of numerous drugs. Also, these dosage forms are large in size due to which don't pass through pylorus (0.9-1.9 cm opening)¹⁷. So, FDDS provides sustained drug delivery.

Site-specific drug delivery

Some drugs such as furosemide, riboflavin show site specific absorption site in the upper part of GIT. In fact, the major site of absorption is stomach for furosemide, followed by the duodenum. So, floating dosage form of furosemide can be beneficial to prolong the GRT, hence it increases the bioavailability¹⁸.

Local action in stomach

The FDDS are beneficial for drugs that are desired to produce local action in the stomach. For example: antacids.

Reduce irritation of acidic drugs

Acidic drugs, after administration may cause irritation on the stomach wall. Hence floating dosage forms may be advantageous for the administration of acidic drugs such as aspirin and other¹⁹⁻²¹.

Advantageous to drugs which are unstable in intestine environment

Drugs such as captopril, ranitidine HCl, metronidazole which are unstable in the intestinal or colonic environment can be

administered by making floating dosage forms²².

Beneficial to drugs that show low solubility at high pH

Some drugs such as diazepam, chlorthalidone, verapamil show low solubility at high pH. FDDS can be useful because it enhances the GRT of these drugs and hence increases the bioavailability of these drugs by increasing absorption.

Pharmacokinetic advantages

FDDS maintain constant blood level because of sustained released nature of these dosage forms, easy in administration and patient compliance is also improved.

DISADVANTAGES OF FDDS

Not feasible for those drugs that have solubility or stability problems in gastric fluids not suitable for the drugs that are irritant to gastric mucosa²³.

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 emptying²⁴.

LIMITATION OF FDDS

These systems are not suitable for those drugs that have solubility or stability problems in the stomach.

There is need of high level of fluid in the stomach for success of these systems.

Drugs which undergo first pass metabolism are not suitable for the FDDS. For example: nifedipine.

Drugs that cause irritation in stomach mucosa are not suitable candidates for FDDS.

APPROACHES TO DESIGN THE VARIOUS FLOATING DOSAGE FORM

Two types of floating dosage systems i.e. single- and multiple-unit floating dosage systems have been designed by using the following approaches²⁵.

SINGLE-UNIT DOSAGE FORMS

Low-density approach

In this approach, the globular shells with density lower than that of gastric fluid can be used as carrier for drug for making single-unit floating dosage form. Popcorn, polystyrol and papipe have been used as drug carriers in coated shells²⁶. For the undercoating of these shells sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been exploited. These shells are then further coated with a mixture of drug-polymer. Depending on the type of release

desired, either of the polymer ethyl cellulose or hydroxypropyl cellulose can be used. The product floats on the gastric fluid and gradually releases the drug for a long period of time.

Fluid- filled floating chamber

In this type of dosage forms, a gas-filled floatation chamber is incorporated into a microporous component that covers the drug reservoir. Along the top and bottom walls there are provision for opening through which the GIT fluid enters into the device to dissolve the drug. The side walls in contact with the fluid are sealed to ensure undissolved drug remains in the device. The fluid present in the system for floatation could be air or any other suitable gas, liquid, or solid that has an appropriate specific gravity and should be inert. This device should be of swallowable size. Device remains floats within the stomach for a long period of time and slowly releases the drug. After the complete release of the drug, the shell disintegrates, goes to the intestine, and finally eliminated from the body²⁷.

Hydrodynamically balanced systems (HBS)

These systems enhance the absorption because they are designed such that they stay in GIT for prolong time. Drugs which have a better solubility in acidic environment and site-specific absorption in the upper part of GIT are suitable candidates for such systems. These dosage forms must have a bulk density of less than 1. It should maintain its structural integrity and should constantly release the drug. The solubility of chlorthalidone hydrochloride²⁹ is 150 mg/mL at pH 3 to 6 and is ~0.1 mg/mL at neutral pH. So, HBS capsule of this drug is a better than conventional one to solve the solubility problem.

Bilayer and matrix tablets

Floatable characteristics also shown by some types of bilayer and matrix tablets. The polymers which have been exploited are sodium carboxymethylcellulose (CMC), hydroxypropyl cellulose, hydroxypropyl methylcellulose, ethyl cellulose and Crosspovidone.

3-layer principle

By the development of an asymmetric configuration drug delivery system²⁸, 3-layer principle has been improved. 3-layer principle helps in modulating the release extent and for achieving zero-order release kinetics. The design of the system is such that it floats on the stomach content and prolong gastric residence time which further results in longer total transit time which maximize the

absorptive capacity and hence better bioavailability is achieved. These benefits can be applicable to drugs with pH-dependent solubility, drugs which are absorbed by active transport mechanism from the small intestine or the drugs with narrow absorption window.

Problems with single-unit formulations

Single-unit formulations can stick together or being obstructed in the GIT, which can cause irritation.

MULTIPLE-UNIT DOSAGE FORMS

Multiple-unit dosage form is designed to develop a reliable formulation that provide all the benefits of a single-unit form and also overcome the disadvantages of single-unit formulations. Microspheres have been used because of their high loading capacity. The polymers such as albumin, starch, gelatin, polyacrylamide, polymethacrylate and polyalkylcyanoacrylate have been used for the preparation of microspheres. Microspheres show an excellent in vitro floatability because of its characteristic internal hollow structure. Several devices of carbon dioxide multiple-unit oral formulations³⁰ have been described in the recent patent literature with features that unfold, extend or are inflated by carbon dioxide generated in the devices after administration.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM³¹⁻⁴¹

EFFERVESCENT SYSTEM

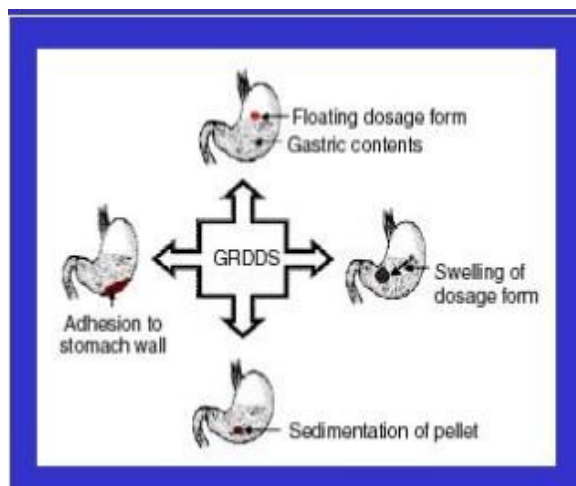
- Gas generating system
- Volatile liquid containing system

NON-EFFERVESCENT SYSTEM

- Colloidal gel barrier system
- Alginate beds
- Hollow microspheres / Microballons
- Intra-gastric 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.



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.

Gas-generating Systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 , which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.

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.

Hollow microsphere

It is prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric polymer was pured 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.

Alginate beads

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 12 hours.

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.

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. 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.

FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS⁴²⁻⁵²

Density of tablets

Gastric retention time (GRT) is depends upon the dosage form buoyancy which is further dependent on the density. Density of the dosage form that is used for FDDS should be less than the gastric contents (1.004gm/ml).

Size and Shape

Dosage form unit with a diameter of more than 7.5 mm are more suitable candidate as compared to those which have a diameter of 9.9 mm because they have an increased GRT. Similarly the dosage form having a tetrahedron shape and ring shape devices 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 and hence more suitable for FDDS as compared with other shapes⁴⁴⁻⁴⁶.

Viscosity of polymer

Viscosity of polymer and their interaction greatly affect the drug release and floating properties of FDDS. Low viscosity polymers (e.g., HPMC K100LV) were found to be more suitable candidates for FDDS than high viscosity polymers (e.g., HPMC K4M) because they improve floating properties. Also, with an increase in polymer viscosity a decrease in the release rate was observed⁴⁸.

Fed or Unfed State

Under fasting conditions, the GRT of the unit is expected to be very short because of the 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 then obviously GRT of the dosage form expected to be very short. But, in the fed state, GRT is considerably longer because MMC is delayed⁴⁹.

Nature of meal

Motility pattern of the stomach can change to fed state when indigestible polymers or fatty acid salts are fed and because of this the gastric emptying rate is decreased and drug release is prolonged⁴⁶.

Frequency of feed

When successive meals are given, the GRT can increase by over 40 minutes compared with a single meal because of the low frequency of MMC⁴³.

Gender

Mean GRT of a male in meals (3.4±0.4 hours) is less compared to the female of the same age and race (4.6±1.2 hours), regardless of the height, weight, and body surface of the two⁴⁵.

Age

Elderly people have a significantly longer GRT, especially those who are over 70 years of age⁵¹.

Posture

Floating forms are protected by an upright position against postprandial emptying because at this position, the floating form remains above the gastric contents irrespective of its size⁵². While the conventional dosage form sink to the lower part of the distal stomach at this position from where they are expelled by antral peristaltic movements through the pylorus. But supine position offers no such protection against early and erratic emptying of floating dosage forms. Only large dosage forms (both conventional and floating) experience prolonged retention when they are anywhere between the lesser and greater curvature of the stomach. On moving distally, these units show significant reduction in GRT compared with upright subjects because of peristaltic movement.

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS⁵³⁻⁵⁶

Determination of hardness of tablet

Randomly sampled twenty tablets in each batch of formulations should be used for the determination of hardness with the help of Monsanto type hardness tester.

Determination of weight variation⁵³

Twenty tablets selected at the random are weighed accurately and the average weight of the tablet is calculated. Then the deviation of individual weight from the average weight is calculated.

Determination of thickness of the tablet⁵⁵

The individual crown – to – crown thickness of ten tablets is determined using slide calipers for each batch.

Measurement of floating capacity⁵⁴

Three individual tablets are put in individual flask containing 400ml of 0.1(N) HCL solutions. Then the time in minutes for each tablets to go from the bottom to the top of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) are measured. The sample mean and standard deviation are then calculated.

Angle of repose⁵⁵

Angle of repose is determined by using funnel method; the accurately weighed spheres are taken in funnel. The height of funnel is adjusted in such a way that the tip of funnel just touches the apex of heap of blends. The blends are then allowed to flow through funnel freely on to surface. The diameter of powder cone was measured; angle of repose is calculated by using following equation.

$$\tan \theta = h/r$$

Where

h– height of pile, θ – angle of repose, r – radius of base pile <25-excellent flow, 25–30-good flow, 30–40- passable,> 40- very poor flow.

Measurement of the density of the formulation⁵⁶

The apparent densities of the tablets are calculated from their volumes and masses in triplicate. The volume V of the cylindrical tablets are calculated from their height h and radius r (both determined with a micrometer gauge) using the mathematical equation for a cylinder ($V = A \times r^2 \times h$).

Determination of drug content in tablets

Three tablets from each batch are selected randomly and transferred to a 100ml volumetric flask filled up with 0.1(N) HCL. Kept it for 48hours then took 1ml from each of volumetric flask and transferred to the test tubes. Samples are then filtered, suitably diluted and analyzed spectrophotometrically at a suitable wavelength.

Determination of in – vitro dissolution study⁵⁶

Dissolution study is carried out in USP –II type dissolution apparatus (paddle type) .Dissolution study was performed at 50 rpm in 900ml 0.1(N) HCL. 5ml of sample was

withdrawn at a predetermined interval and the volume of dissolution medium was maintained by adding same volume of dissolution medium. The absorption of withdrawn sample was measured spectrophotometrically with suitable dilution and the corresponding concentration was determined from the respective calibration curve.

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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