FLOATING TABLET: A REVIEW

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The design of floating drug delivery Systems (FDDS) should be primarily aimed to achieve more predictable and increased bioavailability. Now-a-days most of the pharmaceutical scientist is involved in developing the ideal FDDS. 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. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The place, which cycle both through stomach and intestine every 2 to 3 hours.14 This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC),

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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 (ODDS) 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]. 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 stomach[6] , low density (floating) systems that causes buoyancy in gastric fluid[7-8], mucoadhesive systems that causes bioadhesion to stomach mucosa[10]superporous hydrogel systems[11], unfoldable, extendible or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach[12-13], magnetic systems[14] .

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 controlled [15].

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 side[16]. 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 buoyancy - F 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 remains in the stomach for prolong 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 bioavailability[18]
- **Local action in stomach**

The FDDS are beneficial for drugs that are desire 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 other[19-21].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 forms[22] .

- **Beneficial to drugs that show low solubility at high pH**
  Some drugs such as diazepam, chlordiazepoxide, verapamil show low solubility at high pH. FDDS can be useful because it enhance the GRT of these drugs and hence increase the bioavailability of these drugs by increasing absorption.
- **Pharmacokinetic advantages**
  FDDS maintain constant blood level because of sustain 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 mucosa[23]. 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[24] .

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 under goes 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 approaches[25]

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 poprice have been used as drug carriers in coated shells[26] For the undercoating of these shells sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been exploited. These shells are 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. Hence 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 forms0, a gas-filled floatation chamber is incorporated into a micro porous component that covers the drug reservoir. Along the top and bottom walls there is 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 swalloable 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 body[27]

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 sitespecific 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 chlordiazepoxidehydrochloride[29]is 150 mg/mL at pH 3 to 6and 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 carboxy methylcellulose(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 acheived. 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 a albumin, starch, gelatin, polyacrylamine ,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 formulations[30] 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.

POLYMER [37]

A polymer is a large molecule, or macromolecule, composed of many repeated subunits. Because of their broad range of properties ,both synthetic and natural polymers play an essential and ubiquitous role in everyday life.

CLASSIFICATION OF POLYMER [38]

A .Polymer based on backbone

1) Polymer with carbon chain backbone; polyethyl; poly ene, polypropylene, polystyrene, polyvinyl chloride, polyacrylo. nitrile, poly (vinyl alcohol), poly(vinyl acetate), poly (methyl methacrylate), polyvinylpyrrollidone etc.

2) Polymer with heterochain backbone (ethyleneoxide), poly (propylene oxide), cellulose(poly-glucoside), amylase, pectinic acid, polyethylene glycol terephthalate etc.

B. Natural or synthetic polymer

1. Protein based; albumin, collagen, gelatin.

2. Polysaccharide; carrageen, chitoson, dextran, polysialic acid etc.
3. Synthetic polymer

- **Biodegradable**

a. Polyesters;poly(glycpoly(lactic acid), ponic acid).
b. Polyanhydrides; poly (sebacic acid), poly adipic acid.
c. Polyamides; poly(imino carbonates), polyamino acid
d. Phosphrous–based; polyphosphate,polyphospsphazenes

- **Non-biodegradable**

a. Cellulose derivative; carboxymethylcellulose, cellulose, ethylcellulose
b. Silicones; colloidal silica.

Natural polymer in drug delivery:[39]

These systems are useful to several problems encountered during the development of a pharmaceutical dosage form. Floating drug delivery systems are the gastroretentiveformsthat precisely control the release rate of target drug to a specific site which facilitate an enormous impact on health care. This can be achieved by use of various polymeric substances including natural polymers. These polymers are inexpensive, safe and available in a variety of structures with versatile The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. 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. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application characteristics. Large number of derivatizable groups, wide range of molecular weights, varying chemical composition and gel forming nature of these polymers also provide an exciting opportunities in the fascinating arena of applied polymer science and drug delivery technology. All these characteristics make them suitable candidate for design and fabrication of novel gastroretentive drug delivery systems. Various natural polymers have been investigated worldwide by scientific community for their potential as floating drug delivery systems. The present article highlights various recent efforts and advanced approaches exploiting several natural polymers in this technology.

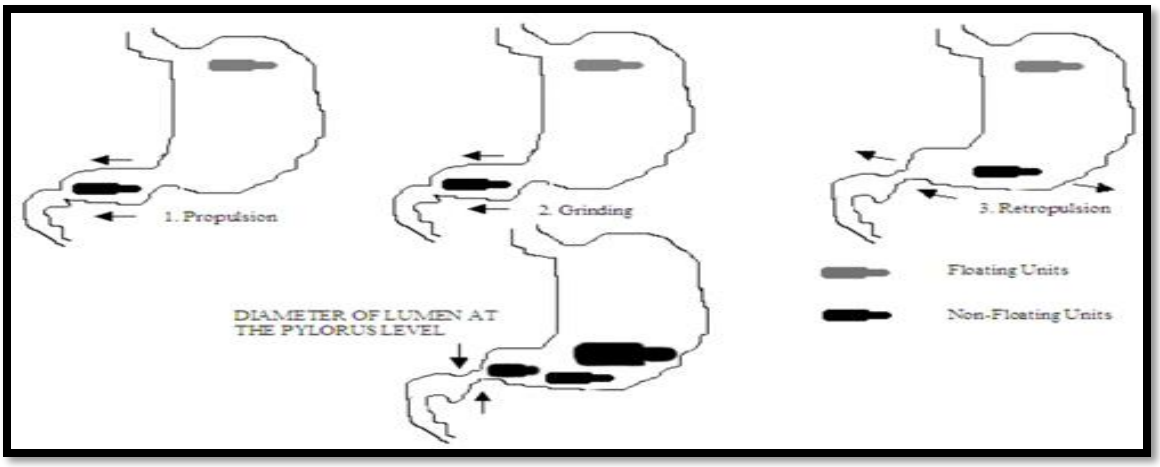

Figure 1: Floating and Non-Floating units in Gastro Intestinal Tract

Floating drug delivery systems are the gastroretentive forms that precisely control the release rate of target drug to a specific site which facilitate an enormousimpact on health care. This can be achieved by use of various polymeric substances including natural polymers. These polymers are inexpensive, safe and availablein a variety of structures with versatile characteristics. Large number of derivatizable groups, wide range of molecular weights, varying chemical composition andgel forming nature of these polymers also provide an exciting o time by altering physiologicaland formulation variables. Several approaches have been tried to retain. The dosage form in the stomach including low density gel forming nature of these polymers also provide an exciting opportunities in the fascinating arena of applied polymer science and drug delivery technology. All these characteristics make them suitable candidate for design and fabrication of novel gastroretentive drug delivery systems. Various natural polymers have been investigated worldwide by scientific community for their potential as floating drug delivery systems. The present article highlights various recent efforts and advanced approaches exploiting several natural polymers in this technology and logical approach in the development of gastroretentive dosage forms. In the last two decades, various attempts have been made to develop a novel and efficient gastroretentive dosage forms which can retain in the stomach for an extended period of time in a predetermined manner. This can be achieved by improving scientific advancements to overcome various physiological problems like pH of the stomach, motility, gastric emptying dosage form (floating dosage form), high density dosage form, bioadhesive dosage form, ion exchange resins, expanding the dosage form by swelling. Out of the above different approaches, the most convenient, economical and effective one is gastric floating drug delivery technology. Floating dosage forms can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of various drugs. Prolonged gastric retention improves solubility of drugs that are less soluble in high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestine. Gastroretention helps to provide better availability of new formulations with suitable therapeutic activity and substantial benefits for patients.

***In – Vitro* Characterization**

1. Weight uniformity test[32]If the drug forms greater part of the tablet, any variation in the tablet weight obviously indicates a variation in the active ingredient this test resembles weight uniformity test. 20 tablets were selected at random and average weights were determined. Then individual tablets weighed and the individual weight was compared with the average.

Average weight of tablets (X) = (X1+X2 +X3+…+ X20) / 20

2. Hardness uniformity studies[32]The hardness of prepared formulation was measured by using Pfizer hardness tester. Five floating tablets were used for hardness uniformity studies. The hardness data used to calculate mean and standard deviation.
3. Thickness uniformity studies:The thickness uniformity studies were carried out by using Vernier callipers. Five tablets were used for thickness uniformity studies and denoted in millimeter. The data obtained was used to calculate mean and standard deviation.
4. Friability (F):The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). 20 tablets were initially weighed (W initial) and transferred into the friabilator. The friabilator was operated at 25 rpm per min for 4 mins (100 revolutions). The tablets were weighed again (W final). The % friability was then calculated .
5. Thickness and diameter [32]:Tablet thickness is important for tablet packaging; very thick tablets affect packaging either in blisters or plastic containers. The tablet thickness is determined by the diameter of the die, the amount of fill permitted to enter the die and the force or pressure applied during compression. The thickness of the tablet may be measured manually or by automatic eq0uipment. The thickness and diameter of the tablets was measured by VernierCalipers. It is expressed in mm.
6. Content uniformity:Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in a suitable solvent and make up the final volume with the suitable buffer solution. The sample was mixedthoroughly and filtered through a 0.45µ membrane filter. The filtered

solution was diluted suitably and analyzed for drug content by UV spectrophotometer, using buffer solution as a blank.

7. In vitro buoyancy / floating study:In vitro buoyancy studies were performed for all the formulations. The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).
8. Swelling Index [33] The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium pH 6.8 buffer at 37 ± 0.5°C. After 0.5, one, two, three, four, five, six, seven and eight hours, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, AX 120). The experiment was performed in triplicate for each time point.
9. Disintegration studies [34] Tablets were randomly selected and one tablet was introduced in each tube disintegration apparatus and placed in 1litre beaker containing water at 37°± 2°C and the time of disintegration was recorded. The study was done at room temperature without disc being added.
10. In vitro dissolution studies[35] The release rate of aceclofenac from floating tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of pH 1.2 HCL buffer for 2 hrs followed by pH 6.8 Phosphate buffer for 8hrs. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with of pH 1.2 HCL buffer for 2 hrs followed by pH 6.8 Phosphate buffer for 8hrs. Absorbance of these solutions was measured at 274 nm using a UV/Visible spectrophotometer.
11. FT-IR spectra [36]:Fourier transform Infra red analysis (FT-IR) measurements of pure drug, polymers and drugloaded floating tablets formulations were obtained using a model name BX- Perkinelmer System 200 FT-IR Spectrophotometer. The pellets were prepared on KBr press under hydraulic pressure of 150 kg / cm2, the spectra were scanned over the wave number range of 4000-400 cm-1 at an ambient temperature.
12. Drug release kinetics [36] The success of HPMCE5M with Eudragit RS100 in controlling the release of the drug was studied under the following heads to understand the order and probable underlying mechanism involved in the release pattern. To analyze the mechanism of drug release from the prepared formulations, the data obtained from in vitro release studies were subjected to Higuchi's model, Zero order model and Korsmeyer's model.

Conclusion

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. 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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