Floating Drug Delivery System

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INTRODUCTION

Floating systems explain that the systems are having low density, having a greater property of buoyancy to float over the gastric fluids present in stomach and help in maintaining of longer action1. Davis first identified floating systems in 1968. They are low-density systems with enough buoyancy to float over the gastric contents and stay in the stomach for an extended period of time2. The drugs which are having short biological half-life, they can be sustained by floating drug delivery system and their efficacy can be increased and help in decreasing the dosing frequency. This aspect of feds is assisting in increasing patient compliance and improving pharmacological therapy3. Based on granules, powders, capsules, tablets, laminated films and hollow micro spheres, several buoyant systems have been developed4. Floating drug delivery systems are intended to prolong the duration of the dose form in the gastrointestinal tract while also assisting in the enhancement of absorption. Drugs that are more soluble in acidic conditions and have a specific absorption location in the upper section of the small intestine are more suited to these mechanisms4. Floating multi-particulate are gastro-retentive drug free-flowing protein or synthetic polymer powders, preferably smaller than 200 micrometres in size. Floating multi-particulate are gastro-retentive drug delivery systems which are based on non-effervescent and effervescent approach. Gastro-retentive systems will remain for several hours in the gastric region and thus significantly extend the drug’s gastric residence time. In a high pH setting, sustained gastric retention increases bioavailability, decreases drug wastes and improves solubility for drugs that are less soluble delivery systems based on non-effervescent and effervescent approach. In a strict sense, hollow microspheres are empty spherical particles without a core5. Sustained release dosage forms are those that provide medication over a long period of time. The term “controlled release” refers to the system’s ability to have some therapeutic control6. It is helpful in maximizing effectiveness and compliance. Usually, normal gastric residence time ranges from 5 min to 2 hrs3. Floating dosage forms are quickly gaining popularity as a promising new dosage form5. Floating dosage forms may be made as tablets or capsules by using appropriate excipients and including gas-generating agents, which give the dosage form buoyancy in gastrointestinal fluids7. The drug is slowly released at the optimal rate from the system while it is floating on the gastric contents. The residual system in the stomach is emptied after the medication is released8.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

A. Single Unit Floating Dosage Systems
   a) Effervescent Systems (Gas-generating Systems)
   b) Non-effervescent Systems

B. Multiple Unit Floating Dosage System
   a) Effervescent Systems (Gas-generating Systems)
   b) Non-effervescent Systems
   c) Hollow Microspheres
C. Raft Forming System

A. Single Unit Floating Dosage Systems

Single unit dosage forms are easier to produce, however due to their all or no emptying from the stomach, they suffer from the risk of losing their effects too early and can therefore cause high variability in bioavailability and local discomfort due to a large volume of drug administered at a specific location of the gastrointestinal tract.

a) Effervescent Systems (Gas-generating Systems)

These are matrix systems of systems that are prepared using swelling polymers such as chitosan and methylcellulose, as well as several effervescent compounds such as sodium bicarbonate, citric acid and tartaric acid. They’re made such that CO2 is produced when it comes into touch with acidic gastric contents and becomes lodged in swollen hydrogels, giving dose kinds buoyancy.

b) Non-effervescent Systems

Non-effervescent floating dosage forms use polysaccharides, hydrogels and matrix-forming polymers such as polyacrylate, polycarbonate, polystyrene and polymethacrylate to form a gel forming or swelling cellulose type. The method of formulation includes a simple approach to thoroughly mixing the drug and the hydrocolloid forming gel. This dosage form swells in contact with gastric fluids following oral administration and achieves a bulk density of < 1. The air trapped within the swollen matrix imparts the dosage shape with buoyancy. The swollen gel-like structure formed in this way acts as a reservoir and allows the gelatinous mass to sustainably release the drug.

Hydroxypropyl methyl cellulose (HPMC), polyvinyl acetate, polyacrylate polymers, sodium alginate, carboxyl, agar, calcium chloride, polyethylene oxide and polycarbonate are the most widely used excipients in these systems.

B. Multiple Unit Floating Dosage Systems

Multiple unit dosage forms may be an appealing alternative, as it has been shown that inter- and intra-subject differences in drug absorption are reduced as well as the risk of dose dumping is reduced. Several multiple unit floating systems were created utilizing concepts such as a multiple unit system of air compartments, hollow microspheres filled with a gel. These are made using the emulsion solvent diffusion method, and beads made using the emulsion gelation process. Another technique for planning multiple unit FDDS is the use of effervescent and swellable polymers.

a) Effervescent Systems

A multi-unit system was created, consisting of a calcium alginate core and a calcium alginate/PVA membrane separated by an air compartment. The PVA leaches out in the presence of water and increases the permeability of the membrane, preserving the integrity of the air compartment. The increase in molecular weight and PVA concentration has resulted in the improvement of the system’s floating properties. The technique of freeze-drying for the preparation of floating calcium alginate beads is also mentioned. Sodium alginate solution, due to the formation of calcium alginate, is applied drop wise into the aqueous solution of calcium chloride, allowing the droplet surface to instantly gel. The beads obtained are freeze-dried, leading to a porous structure that assists in floating. The researchers explored the behavior of radiolabelled floating beads and used gamma scintigraphy in contrast to non-floating beads in human volunteers. For floating beads, prolonged gastric residence time was observed in excess of 5.5 h. With an overall emptying time of 1 hr, the non-floating beads had a shorter residence time.

b) Non-effervescent Systems

In contrast with the effervescent systems, there was not much study on effervescent multiple unit systems found in the literature. Few workers, however, have documented the possibility of creating such an indomethacin-containing method, using chitosan as the polymeric excipient. A multiple HBS unit containing indomethacin is recorded as a model drug prepared by the extrusion process. Via the blade, a mixture of drug, acetic acid and chitosan, is extruded and the extrudate is cut and dried. In the acidic media, chitosan hydrates and floats, the requisite drug release could be achieved by changing the ratio of drug-polymer.

d) Hollow Microspheres

In their outer polymer shell, hollow microspheres filled with drugs were prepared using a novel method of emulsion solvent diffusion. The drug’s ethanol/dichloromethane solution and enteric acrylic polymer were poured into a thermally controlled agitated Poly Vinyl Alcohol (PVA) solution at 40°C. The evaporation of the dichloromethane created in the dispersed polymer droplet and the interior cavity in the drug polymer microsphere produces the gas phase. The micro-balloon floated continuously over the surface of a surfactant containing acidic dissolution media for more than 12 hours. Hollow microspheres are one of the most promising buoyant structures because of the core hollow area within the microsphere, since they have the unique advantages of many unit systems as well as enhanced floating attributes.

C. Raft Forming System

Here, a gel-forming solution (e.g., carbonate or bicarbonate-containing sodium alginate solution) swells and forms a viscous cohesive gel on contact with gastric fluid containing trapped CO2 bubbles. Antacids such as calcium carbonate or aluminium hydroxide are often usually used in formulations to minimize gastric acidity. They are also used for gastro-oesophageal reflux treatment since raft forming systems create a coating on the top of gastric fluids. The preparation of a viscous cohesive gel in contact with gastric fluid, where the liquid swells in each part, forming a continuous layer known as a raft, is one of the mechanisms involved in raft formation. This raft floats on stomach juices due to its low density and the production of carbon dioxide.

ADVANTAGES

1. Also at the alkaline pH of the intestine, floating drug types such as capsules or tablets will stay in the solution for an extended period.

2. The drugs which are absorbed through the stomach, for them the gastro-retentive system is advantageous. E.g., Ferrous salts, and antacids.

3. When an acidic substance like aspirin meets the stomach wall, it causes discomfort. As a result, HBS/FDDS formulations could be useful for administering aspirin and other comparable medications.

4. FDDS dosage forms are beneficial in cases of diarrhoea and vigorous intestinal movement because they keep the drug in a floating state in the stomach, allowing for a better response.

5. For drugs ingested through the stomach, the FDDS is beneficial, e.g.: ferrous salts, antacids. Improved drug
absorption due to increased GRT and more time spent on its absorption site by the dosage type\textsuperscript{13}.

6. FDDS are advantageous for those drugs which provide local irritation to the stomach. eg: Antacids\textsuperscript{13}.

7. FDDS are having advantage for Treating the gastrointestinal disorders such as gastroesophageal reflux\textsuperscript{13}.

8. Ease of administration and patient compliance\textsuperscript{14}.

9. Reduces the frequency of dosing\textsuperscript{14}.

10. It enhances the bioavailability of drugs\textsuperscript{15}.

11. Increased bioavailability for medications that can be metabolised in the upper GI tract\textsuperscript{16}.

12) Because of the sustained release effect, floatability, and uniform release of the drug via the multi-particulate system, there is no gastric irritation\textsuperscript{17}.

13) It is useful in treating gastroesophageal reflux disorder (GERD)\textsuperscript{3}.

14) Advantageous in case of diarrhoea\textsuperscript{18}.

**DISADVANTAGES**

1. Various Factor like gastric motility, pH and presence of food influences the gastric retention and these are never constant. So, the buoyancy can’t be predicted\textsuperscript{18}.

2. The drugs which cause irritation to the gastric mucosa are not suitable for formulating the floating drug delivery system\textsuperscript{18}.

3. In sleeping subject, the gastric emptying of floating tablets may occur at random. Hence the patient should avoid the floating tablet dose just before going to bed\textsuperscript{19}.

4. Drugs having solubility and stability problem in gastric fluids are not suitable for formulating floating drug delivery system\textsuperscript{19}.

5. For the drug to float and work efficiently, it requires high level offield in the stomach\textsuperscript{20}.

6. The drugs which undergo first pass metabolism are not suitable for preparing the floating drug delivery system\textsuperscript{19}.

7. The drugs which are unstable in the acidic environment of stomach are not suitable for formulating the floating drug delivery system\textsuperscript{20}.

8. In the case of children and unconscious patients, swallowing is a problem\textsuperscript{21}.

**MECHANISM OF FDDS**

- FDDS have a lower bulk density than gastric fluid, so they stay buoyant in the stomach for a extended period of time without impacting the gastric emptying rate. While the systems are floating on the gastric material, the drug is slowly released from the system at the required rate.

- To keep the dose form buoyant on the surface of the meal, a minimum level of floating force (F) is necessary.

- A new apparatus for determining the resulting weight has been recorded in the literature for the calculation of floating force kinetics. The apparatus operates by continuously measuring the force that is needed to sustain the submerged object, equivalent to F (as a function of time)\textsuperscript{22}.

- In order to avoid the disadvantages of unforeseeable variations in intragastric buoyancy performance, this system helps to optimize FDDS with regard to the stability and durability of floating forces generated.

- The drug is released slowly and at the optimal rate from the system while it is floating on the gastric material\textsuperscript{23}.

**FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM**

1) **Density of the dosage form.**

- Floating is dependent on density. The density of dosage form must be less than the gastric content (1.004 gm/ml).

- So, density of less than 1gm/ml is required to show the floating property.

- Therefore, dosage form having a density lower than the gastric content can easily float on the surface while higher density dosage forms sink to the bottom of the stomach.

2) **Shape and size of dosage form**

- Increases in gastric retention time (GRT) relative to those with a diameter of 9.9 mm are recorded for dosage type units with a diameter greater than 7.5 mm.

- With a flexural module of 48 and 22.5 kilo pounds per square inch (KSI), the dosage form of tetrahedron and ring shape designs was stated to exhibit better GIT for 90 to 100 percent retention at 24 hours compared to other shapes.

3) **Food intake and its Nature**

- Feed intake, food viscosity and volume, caloric content and feeding frequency have a significant effect on the stomach retention of dosage types.

- The presence or absence of food in the gastrointestinal tract influences the gastric retention time (GRT) of a dose type (GIT). Feeding indigestible polymers or fatty acid salts to the stomach may cause the motility pattern to shift to a fed state, resulting in a slower gastric emptying rate and longer medication release.

4) **Caloric content**

- With a meal that is rich in proteins and fats, the gastric retention time (GRT) can be increased by 4 to 10 hours.

- Due to the low frequency of migrating myoelectric complexes, floating will increase by over 400 minutes when successive meals are given compared to a single meal (MMC).

5) **Effect of gender, posture and age**

- Females experience slower rates of gastric emptying than males.

- The influence of posture does not vary much more in the meantime of gastric retention (GRT).

- Gastric emptying is slowed down in the case of elderly individuals, especially those over 70, who have a significantly longer GRT.

6) **Fed or unfed condition**

- Periods of intensive motor activity during fasting conditions or the migrating myoelectric complexes...
(MMC) that occur every 1.5 to 2 hours characterise gastric motility.

- The MMC sweeps undigested material from the stomach, and it can be predicted that the GRT of the unit is very short if the timing of administration of the formulation corresponds with that of the MMC. However, MMC is delayed in the fed state and GRT is slightly longer.

7) Concomitant drug administration

- Floating time can be affected by anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents such as metoclopramide and cisapride.

8) Single or multiple unit formulation.

- Leading to the failure of the units, multiple unit formulations are more predictable, allow co-administration of units with various release profiles or containing incompatible substances and allow a greater safety margin against failure of the dosage form compared to single unit dosage forms24.

9) Biological factors

- Biological factors like Diabetes and Crohn’s disease affect the floating drug delivery system25.

10) Volume of liquids

- The stomach’s resting volume is 25 to 50 ml. The amount of liquids given has an impact on the time it takes for the stomach to empty. When the volume is high, the emptying process is accelerated. Fluids that are taken at body temperature exit the stomach quicker than fluids that are cooler or warmer26.

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS

1. Enhanced Bioavailability

In contrast to the administration of non-GRDF CR polymeric formulations, riboflavin CR-GRDF has a substantially higher bioavailability. There are many mechanisms that function in concert to affect the degree of drug absorption, including drug absorption and transit in the gastrointestinal tract.

2. Sustained Drug Delivery

Problems with gastric residence duration in the Gastrointestinal Tract (GIT) have been reported with oral controlled release formulations. These issues can be solved by HBS systems, which can stay in the stomach for long periods of time and have a high bulk density.

3. Site-Specific Drug Delivery Systems

These systems are especially useful for medications that are absorbed predominantly through the stomach or the proximal small intestine. The monitored, gradual delivery of the medication to the stomach ensures sufficient local therapeutic levels while limiting the drug’s systemic exposure. The drug’s side effects in the blood supply are minimised as a result. Furthermore, a site guided delivery system’s prolonged gastric availability can reduce dosing frequency. For instance, furosemide and riboflavin.

4. Absorption Enhancement

Drugs having low bioavailability due to site-specific absorption from the upper part of the GIT may be formulated as FDDS to improve absorption.

5. Minimized Adverse Activity At The Colon

The amount of drug that enters the colon is decreased when the drug is stored in the Hydrodynamically Balanced system (HBS) systems at the stomach. Hence, the drug’s undesirable effects in the colon can be avoided. The justification for Gastro-retentive dosage form (GRDF) formulation for beta-lactam antibiotics that are absorbed only from the small intestine and whose presence in the colon contributes to the production of microorganism resistance is based on this pharmacodynamic aspect.

6. Reduced Fluctuations Of Drug Concentration

In contrast to immediate release dosage types, continuous input of the medication after controlled release gastro-retentive dosage form (CRGRDF) administration induces blood drug concentrations within a narrower range. Thus, Drug effect variations are decreased, and concentration-dependent side effects associated with peak doses can be avoided. This is especially important for drugs with a small therapeutic index27.

DRUG CANDIDATES SUITABLE FOR FDDS:

- Drugs having narrow absorption window in GIT (e.g., L-DOPA, furosemide, P-amino benzoic acid, riboflavin)
- Drugs which are locally active in the stomach (e.g., antacids, misoprostol)
- Drugs which are unstable in the intestinal environment (e.g., Metronidazole, rantidine HCI, Captopril)
- Drugs having ability to affect normal colonic microbes (e.g., antibiotics used for the eradication of Helicobacter pylori, such as Clarithromycin, tetracycline, amoxicillin)
- Drugs having low solubility at high pH values (e.g., verapamil, diazepam, chlorzoxazone)28.

POLYMERS USED FOR FLOATING DRUG DELIVERY SYSTEM.

- Casein
- Cellulose acetate
- Chitosan and Sodium alginate
- Eudragit
- Polyvinyl alcohol
- Polycarbonate10

METHOD OF PREPARATION

1) Solvent evaporation method

- The floating multi-particulate dosage form was prepared using solvent diffusion and evaporation methods to create a hollow inner core. After dissolving the polymer in an organic solvent, the drug is dissolved in the polymer organic solution.
- The drug solution is then emulsified into an aqueous phase containing Polyvinyl alcohol (PVA) to create an O/W emulsion. Then the organic solvent is evaporated by increasing the temperature or stirring continuously.
- The removal of the solvent causes polymer to precipitate at the oil in water (O/W) interface of droplets, forming a cavity and making them hollow, allowing them to float.
- Cellulose acetate, polyvinyl acetate, Chitosan, Acrycoat, Eudragit, Methocil, Polycrylates, Polycarbonates,
Carbopol, Polyethylene oxide, and Agar are among the polymers being considered for the construction of such floating systems.

- Theophylline (as the model drug), Polypropylene foam powder and Eudragit RS, ethyl cellulose, or polymethylmethacrylate (PMMA) were used to make floating microparticles using an O/W solvent evaporation process.
- Methylene chloride was used to dissolve the rate-controlling polymer and drug. The polypropylene powder was then spread within the organic phase that had been prepared.
- Then, the final suspension was emulsified in an aqueous polyvinyl alcohol (PVA) solution. The microparticles were sieved and rinsed in cold water before being dried in a desiccator with sufficient silica gel; they are all irregular in shape and size and have a porous structure.
- The drug combining efficiency was generally high and nearly independent of the theoretical drug loading assumption in the method. The assessment of formulations will provide a wide range of drug release patterns.
- Fast preparation time, no exposure of the product to high temperatures, a propensity to prevent toxic organic solvents, and high drug combining efficacy are all advantages of this novel preparation technique (near to 100 percent).
- Polymer foam powder, a model drug (e.g., Chlorpheniramine maleate), and a secondary polymer [Poly(methyl methacrylate)] make up a floating microparticle framework. They were made by soaking microporous foam particles in an organic solution that contained both the medication and the polymer.
- The low-density microparticles may also be compressed into fast-dissolving capsules, resulting in a conveniently administrable oral dosage type.

### 2) Ionotropic Gelation Method

- The tendency of polyelectrolytes to cross connect in the presence of counter ions causes ionotropic gelation, which results in the formation of beads. This gelation technique has been commonly used for the preparation of beads since the use of Chitosan, Alginates, CMC, and Gellan gum for drug encapsulation.
- By combining with polyvalent cations, these anions form mesh-like structures and insert gelation by combining primarily with anion blocks. Dropping a drug-loaded polymer solution into a polyvalent cationic aqueous solution produces hydrogel beads.
- To preserve the 3D structure of these beads, biomolecules can be introduced under mild conditions.

### 3) Emulsion solvent diffusion method

- Micro-balloons (hollow microspheres) with drug in their outer polymer shell, made using a new emulsion solvent diffusion process. A polymer and drug solution in ethanol methylene chloride is poured into an agitated aqueous polymer solution (vinyl alcohol).
- The entrapped methylene chloride evaporates, resulting in the creation of internal cavities within the microparticles.

### EVALUATION OF FLOATING TABLET

#### Weight variation test

Twenty tablets were chosen at random from each batch and measured separately to see if there was any weight difference. The USP allows for small variation in the weight of a tablet. The percentage deviation in weight variance allowed is as follows. The tablet weight was greater than 324 mg in all formulations, allowing for a maximum difference of 5%.

#### Hardness test

The hardness of a tablet determines its ability to endure mechanical shocks while being treated. The Monsanto tester was used to assess the hardness (kg/cm²) tablet. The average of five replication determinations was used in all cases.

#### Friability test

This was determined by weighing 26 pills after dusting, placing them in the Roche friabilator, and rotating the plastic cylinder vertically at 25 rpm for four minutes, according to Indian Pharmacopoeia (IP). The total remaining weight of the tablets was reported after dusting, and the percentage friability was calculated using the equation below.

\[
\% \text{ Friability} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets} \times 100}
\]

The acceptable friability of tablets is < 1%.

#### In vitro buoyancy study

The period between the introduction of the dosage form and its buoyancy on the SGF, as well as the time the dosage form stays buoyant, were all measured. The time it takes for the dosage form to appear on the medium’s surface is known as Floating Lag Time (FLT) or Buoyancy Lag Time (BLT), and the total time it takes for the dosage form to stay buoyant is known as Total Floating Time (TET). Floating behaviour study were carried out in a USP XXIII dissolution Apparatus type II (Paddle) at a speed 50 RPM in 900 ml SGF at 37±0.50°C for 12 hr to mimic in vivo conditions.

#### X-Ray method

Nowadays, X-Ray has become a very common evaluation parameter for floating dosage forms. It aids in the location of dosage forms in the GIT, as well as the prediction and correlation of gastric emptying time and dosage form passage in the GIT. The incorporation of a radio-opaque substance into a solid dosage shape allows for X-ray visualisation.

#### Swelling index

The weight assignment determines the swelling activity of the measurement device. When using a pH 6.8 buffer dissolution medium at 370.5 °C, the tablet swelling index correlates to the tablet site in the dissolution tool basket (type 1). At each time point, the trials were repeated three times.

#### Tablet dimension

A calibrated vernier calliper was used to measure thickness and diameter. Three tablets of each formulation were chosen randomly, and their thicknesses were determined separately.

#### Tablet density

Tablet density is considered as an important parameter for floating tablets. The tablet will float only when its density is
less than that of gastric fluid (1.004). We can determine the density using following formula\textsuperscript{32},

\[ V = \frac{2}{3} \pi h d = \frac{m}{v} \]
\[ v = \text{Tablet's volume (cc)} \]
\[ r = \text{Tablet's radius (cm)} \]
\[ h = \text{Tablet's crown thickness (g/cc)} \]
\[ m = \text{Tablet's mass} \]

**CONCLUSION**

The objective of floating drug delivery system (FDDS) is to improve the bioavailability of the drug with narrow absorption window in the gastric region. FDDS is helpful in reducing the frequency of dosing. However, there are many aspects which can be improved to achieve prolonged gastric retention.

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