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A BASIC REVIEW ON FLOATING TABLETS

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ABSTRACT

This article is intended to provide an overview of floating drug delivery systems [FDDS]. Floating tablets prolong the gastric residence times of drugs, improve bioavailability and facilitate local drug delivery to the stomach. Floating drug delivery systems or hydro dynamically balance systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach for a prolonged period of time. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration.

KEYWORDS: Floating drug delivery, gastro retentive drug delivery.

INTRODUCTION

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that are locally active in the stomach, have narrow absorption window in gastrointestinal tract, are primarily absorbed from stomach and upper part of GIT, are unstable in the intestinal or colonic environment, disturb normal colonic bacteria and exhibit low solubility at high pH values.[1-5] Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. Lafutidine has newly developed 2nd generation H2 antihistaminic blocker. It is exceedingly helpful in gastric and duodenal ulcers. It prevents the gastric mucosal lesions in both acute and chronic gastritis. The lafutidine penetrates the stomach wall and binds the H2 receptors. The lafutidine also increases the blood flow to gastric mucosa.[6,7]

Floating drug delivery systems [FDDS]

FDDS is also known as hydro dynamically balanced system [HBS]. While the system is floating on the gastric contents, the drug is release is slowly at the desired rate from the systems. After release of drug, the residual system is emptied from the stomach. This result in an increased GRT and a better control of the fluctuations in plasma drug concentration.

Advantage of FDDS[8-11]

1. Controlled delivery of drugs.
2. Improve drug absorption, because of increased gastro retentive and more time spent by the dosage form at its absorption site.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux
6. Ease of administration and better patient compliance.
7. Site-specific drug delivery.

Limitations of FDDS[12-15]

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process.
4. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.

Approaches to design single and multiple unit dosage form

1- Single unit floating dosages system

In low density approaches, the globular shells apparently having lower density than that of gastric fluid can be used as a carrier like popcorn, pop rice, polysterol for the drug for its controlled release. The polymer of choice can be either Ethyl cellulose or HPMC depending on type of release desired. Finally the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid filled floating chamber type of dosage forms includes incorporation of a gas filled floatation chamber in to a micro porous component that houses as a reservoir having apertures present at top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug.[16] Hydro Dynamically Balanced Systems are designed to prolong the stay of the dosage forms in the gastric intestinal tract and aid in enhancing the absorption. Drugs having a better solubility in acidic environment and also having specific site of absorption in the upper part of small intestine is achieved by these HBS systems. To retain in stomach for a prolonged period of time the dosage form must have bulk density of less than '1' and has to maintain its structural integrity and release drug constantly from the dosage form. Among all the advantages single-unit formulations are associated with some limitations/problems such as sticking together or being obstructed in the GIT which may lead to potential danger of producing irritation.[17]

2- Multiple unit floating dosages systems

Multiparticulate dosage forms are gaining much favor over single-unit dosage forms. The potential benefits include increased bioavailability; predictable, reproducible and generally short gastric residence time, no risk of dose dumping; reduced risk of local irritation, and the flexibility to blend pellets with different compositions or release patterns. Because of their smaller particle size these systems are capable of passing through the GI tract easily, leading to less inter- and intra-subject variability. However, potential drug loading of a Multiparticulate system is lower because of the proportionally higher need for excipients (e.g., sugar cores). Most Multiparticulate Pulsatile delivery systems are reservoir devices coated with a reputable polymeric layer. Upon water ingress, drug is released from the core after rupturing of the surrounding polymer layer, due to pressure build-up within the system.[18] The pressure necessary to rupture the coating can be achieved with swelling agents, gas producing effervescent excipients or increased osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time. Water soluble drugs are mainly released by diffusion; while for water insoluble drug, the release is dependent on dissolution of drug.[19]

Types of FDDS

Based on the mechanism of buoyancy, two distinctly different technologies i.e. non-effervescent effervescent system have been utilized in the development of FDDS;

1- Non-effervescent FDDS.
2- Effervescent FDDS.

1- Non-effervescent FDDS

The FDDS belonging to this class are usually prepared from gel-forming or highly swell able cellulose type hydrocolloids, polysaccharide or matrix forming polymer like polyacrylate, polycarbonate, polystyrene and poly-methacrylate. The drug in the dosage form dissolves in and diffuses out with the diffusing solvent forming a 'receding boundary' within the gel structure.[20,21] This various types of this system are as;

- Single layer floating tablets
- Bi-layer floating tablets
- Alginate beads
- Hollow microspheres

Single layer floating tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity.[22]

Bi-layer floating tablets

A bi-layer tablet contains two layers one immediate release layer which release initial dose from a system while another sustained release layer absorb gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.[23]

Alginate beads

In which 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 ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time which is more than 5.5 hours.[24]

Hollow microspheres

Hollow microspheres (micro balloons), loaded with a drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The micro balloons floated continuously over the surface of acidic dissolution media containing the surfactant for more than 12 hours in *vitro.*[25]

2- Effervescent FDDS

The buoyant delivery system utilized matrices prepared with swellable polymers such as Methocel or polysaccharides (e.g. chitosan) and effervescent components (e.g. Sodium bicarbonate and citric acid or tartaric acid) or matrices having chambers of liquid that gasifies at body temperature.

These effervescent systems further classified into two types.

1- Gas Generating systems
2- Volatile Liquid/Vacuum Containing systems.

Gas- Generating Systems

Intra Gastric Single Layer Floating Tables or Hydro dynamically Balanced Systems (HBS)

These are formulated by intimately mixing the CO2 generating and the drug within the matrix tablet. The drug is slowly released at a desired rate from the floating system and after the complete release; the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.[26]

Volatile Liquid/ Vacuum Containing Systems

- Intra-gastric Floating Gastrointestinal Drug Delivery System
- Inflatable Gastrointestinal Delivery Systems
- Intra-gastric Osmotically Controlled Drug Delivery System

Raft Forming Systems

RFS have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids, described an antacid raft forming floating system. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus.[27]

Factors affecting the floating and floating time

1. **Density:** Floating is a function of dosage form buoyancy that is dependent on the density. Density of the dosage form should be less than the gastric contents (1.004gm/ml).[28]
2. **Shape of dosage form**: Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. Tetrahedron and ring shaped devices with flexural modules of 48 and 22.5 kilo pounds per square inch are reported to have better floating, 90% to 100% retention at 24 hours compared with other shapes.[11]
3. **Concomitant drug administration**: Anti-cholinergic like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.
4. **Fed or unfed state:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (mmc) that occurs in 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, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.[8]
5. **Nature of meal:** Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.[15]
6. **Caloric content and feeding frequency:** Floating can be increased by four to 10 hours with a meal that is high in proteins and fats. The floating can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency.
7. **Age:** Elderly people, especially those over 70, have a significantly longer; floating. Disease condition such as diabetes and crohn's disease etc also affect drug delivery.
8. **Gender:** Mean ambulatory GRT in males (3.4 0.6 hours) is less compared with their age and race-matched female counter parts (4.6 1.2 hours), regardless of the weight, height and body surface.[19]

Method to prepare floating tablets[18]

Tablets are commonly manufactured by three methods.

- Direct compression
- Wet granulation
- Dry granulation

Direct compression

The materials which are available in crystalline form and free flowing and binding characteristics can be compressed directly but the most of the drug cannot be compressed easily in this process because they may be disintegrate. Some vehicles use in this method like calcium phosphate, microcrystalline cellulose, mannitol, anhydrous lactose.[29]

Wet granulation[17]

1. Weighing and blending.
2. Wet granulate prepared by adding the binder solution.
3. Screening the damp mass into pellets or granules (6-8) mesh.
4. Drying the granulation in thermostatically controlled ovens.
5. Dry screening.
6. Mixing with other ingredients (dry binder, colorant, or disintegrate may be also added).
7. Tableting:- last step in which the tablet is fed into the die cavity and then compressed.

Evaluation methods

The prepared floating tablets should be evaluated for following parameter.

- **Thickness**

Thickness can be measured by vernier caliper. Five tablets of the formulation should be picked randomly. This process is frequent time.

- **Hardness or crushing strength**

Hardness can be measured by Monsanto hardness tester or Pfizer. In this process three (3) tablets should be tested for every batch.

- **Friability test**

In this evaluation method twenty (20) tablets should be weigh and placed in the Roche friabilator and apparatus rotate at 25 rpm for 4 minutes. After revolutions, the tablets can dedust and weigh again. The measure % friability using formula.[21]

% F = (initial wt.–final wt.) / initial wt × 100

Where, F = friability in percentage

- **Weight variation test**

Ten (10) tablets randomly select from each batch and weigh individually. Calculate the average weight and standard deviation of twenty tablets. The individually wt. compare with the average weight.

- **In Vitro- Disintegration time**

Tablets place in each six tubes of basket in disintegrations test apparatus. Occlude the assembly in 0.1 N HCL maintained at room temperature of 37 ± 2ºC and operate the apparatus, simultaneously note the time taken to disintegrate completely by using stop watch.[16]

- **In Vitro Buoyancy Studies**

The tablets were placed in a 250 ml beaker, containing 200 ml of 0.1 N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the time period up to which the tablet remained buoyant is determined as total floating time (TFT).

- **Drug content uniformity**

Drug content can be evaluated by using UV-visible spectroscopy and HPLC technique.[15]

Application of floating drug delivery system

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability.

These are summarized as follows

1. Sustained Release Drug Delivery System:- HBS systems can remain in the stomach for long periods and, hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited e.g. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo.

The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).[30]

2. Site-specific drug delivery:- These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g. riboflavin and furosemide e.g. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.[31]

3. Absorption Enhancement:- Drugs that 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 e.g. a significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).[32]

Example of floating tablets

1-Chlorpheniramine maleate	2-Theophylline
3-Furosemide	4-Ciprofloxacin
5-Pentoxyfillin	6-Captopril
7-Acetyl salicylic acid	8-Nimodipine
9-Verapamil HCL	10-Sotalo
11-Atenolol	12-Acetaminophen
13-Ampicilin	14-Cinnarazine
15-Diltiazem	16-Florouracil
17-Prednisolone	18-Riboflavin-5 phosphate

Marketed product list of FDDS

Sr. no.	Brand name	Drug(dose)	Company,country	Remarks
1	Madopar ®	Levodopa(100mg), benserazide(25 mg)	Roche products, USA	Floating CR capsule
2	Valrelease ®	Diazepam (15mg)	Hoffmann-LaRoche, USA	Floating capsule
3	Liquid Gaviscon®	Al hydroxide (95mg), Mg carbonate(358mg)	Glaxo Smith kline ,india	Effervescent floating liquid alginate
4	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate
5	Conviron®	Ferrous sulfate	Ranbaxy, India	Colloidal gel forming FDDS
6	Cifran OD®	Ciprofloxacin (1mg)	Ranbaxy, India	Gas-generating floating tablet
7	Cytotec®	Misoprostal(100mcg/ 200mcg)	Pharmacia, USA	Bilayer floating capsule
8	Oflin OD®	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet

CONCLUSION

The floating drug will significantly extend the period of time over which drugs may be released and thus prolonged dosing intervals and increasing the patient compliance .FDDS promises to be potential approach for gastric retention. Dosage form with prolonged GIT will bring about new and important therapeutics actions.

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