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Review on floating drug delivery system

Raghvendrabadore*,Sanjay harod, Prabhatkumar, Narendra singh and Sujitpillai
Email: badoreraghvendra@gmail.com

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I. INTRODUCTION:

The idealized objective of any drug delivery pinpoints two critical aspects of utmost importance i.e. spatial placement and temporal delivery. Drug delivery system is becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biological parameters pertinent to their performances.[1] Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. Drug delivery patent protected formulation technologies that modify drug release profile, absorption, distribution and elimination of the drug and improving product efficacy, safety, patient convenience and compliance. Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. The primary aim an oral controlled drug delivery system (DDS) should be to achieve more predictable and increased bioavailability of drugs. However, several physiological difficulties preclude the development process.[2] The aim of drug delivery system is to afford a therapeutic amount of drug to the proper site in the body to attain promptly and then maintain desired drug concentration. The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems.[3] The real challenge in the development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time Indeed, gastric drug retention has received significant interest in the past few decades. Most of the conventional oral delivery systems have shown some limitations related to fast gastric emptying time.[4] The successful development of oral controlled drug delivery systems requires an understanding of the two aspects of the system, namely.

1. The physiochemical characteristics of the drug
2. Anatomy and physiology of GIT and Characteristics of Dosage Forms.[5]

Floating Drug Delivery System: Floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid and thus remain buoyant in stomach for prolong period. Floating drug delivery systems (FDDS) or controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased Gastric retention time and a better control of the fluctuations in plasma drug concentration.[6] The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substance. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract and drugs that are less soluble in or are degraded by the alkaline pH may benefit from prolonged gastric retention. In addition, for local and sustained drug delivery to the stomach and proximal small intestine to treat certain conditions, prolonged gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability and therapeutic efficacy, and possible reduction of dose size.[7]

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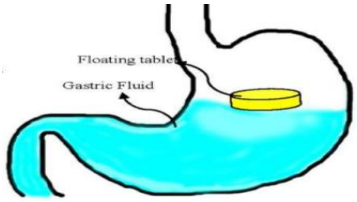

Fig.1 Floating Drug Delivery System

Anatomy And Physiology Of Stomach

The stomach is located in the upper left-hand portion of the abdomen just below the diaphragm. It is a 'J' shaped enlargement of the GI tract directly inferior to the diaphragm in the epigastric, umbilical and left hypochondria regions of the abdomen.[8] Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.[9]

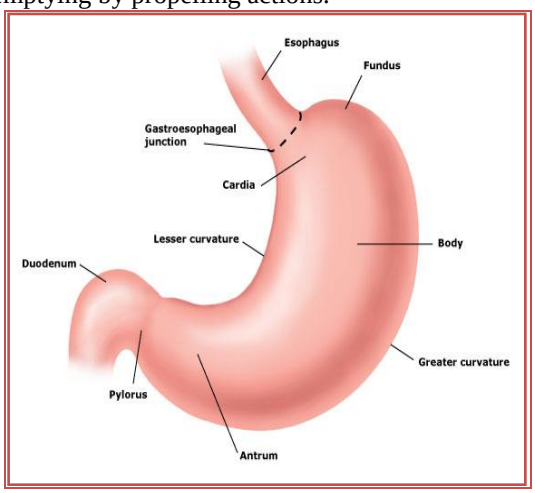

Fig.2 : Structure of Stomach

Gastric emptying : Gastric emptying occurs during fasting as well as fed states. Thepattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.

This is called the interdigestivemyloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases.

1) Phase I (Basal phase) lasts from 30 to 60 minutes with rare contractions.
2) Phase II (Preburst phase) lasts for 20 to 40 minutes withintermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3) Phase III (burst phase) lasts for 10 to 20 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4) Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.[10]

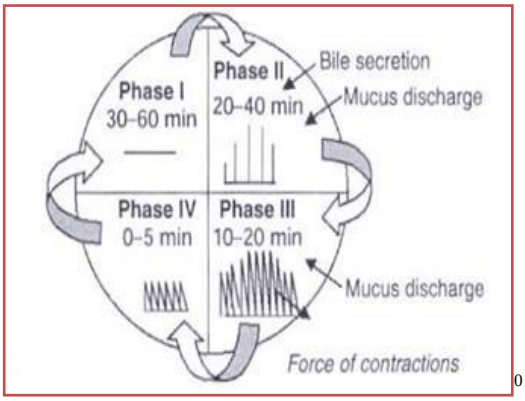

Fig3: Phases of gastric emptying

MECHANISM OF FLOATING SYSTEMS

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), muco adhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (given in the Figure 4 (a)), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy

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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 (Figure 4 (b)). 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.[11]

F = F buoyancy - F gravity

=(Df - Ds) gv--- (1)

Where, F= total vertical force,

Df = fluid density

Ds = object density,

v = volume

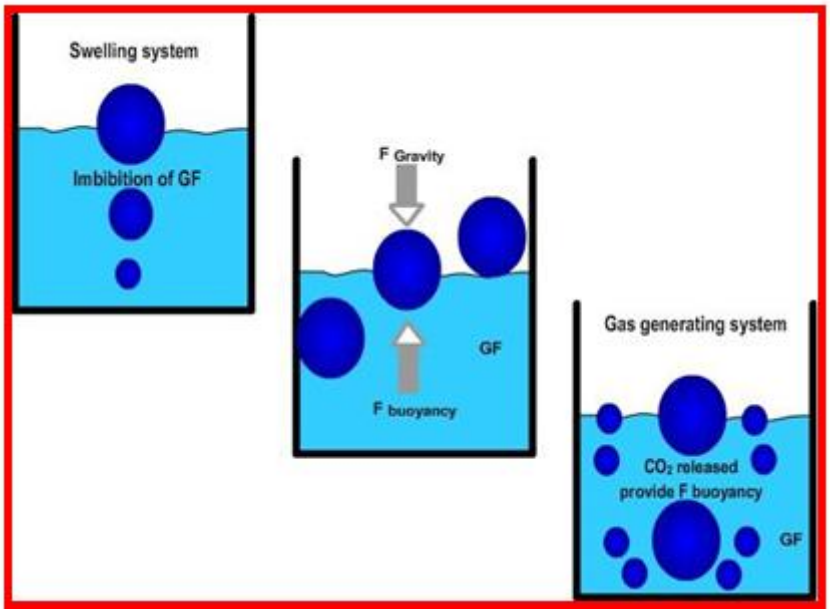

Fig.4: Mechanism of floating systems, GF = Gastsric fluid

SUITABLE DRUG CANDIDATES FOR GASTRO RETENTION:

1. Narrow absorption window in GI tract, e.g., Riboflavin and Levodopa.
2. Primarily absorbed from stomach and upper part of GI tract, e.g., Calcium supplements, Chlordiazepoxide and Cinnarazine.[12]
3. Drugs those are poorly soluble at an alkaline pH.
4. Drugs that is unstable in the intestinal or colonic environment. e.g. Ranitidine HCl and Metronidazole.
5. Drugs with variable bioavailability. E.g. Sotalol HCl.[4]
6. Drugs having low pKa, which remains unionized in stomach for better absorption.
7. The bioavailability of drugs that get degraded in alkaline pH can be increased by formulating gastro-retentive dosage forms, e.g. Doxifluridine, which degrades in small intestine.[7]

ADVANTAGES OF FDDS:

1. The gastroretentive systems are advantageous for drugs absorbed through the stomach, e.g. Ferrous salts, Antacids.
2. Sustained drug delivery and reduced frequency of dosing. This improves patient compliance.
3. FDDS improves patient compliance by decreasing dosing frequency.
4. Better therapeutic effect of short half-life drugs can be achieved.
5. Gastric retention time is increased because of buoyancy.
6. Enhanced absorption of drugs which solubilize only in stomach.
7. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.[13]

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Disadvantages of FDDS:

1. Drugs, that undergo significant first pass metabolism, are not desirable candidate.
2. Drugs having solubility or stability problems in the highly acidic gastric environment cannot be formulated as GRDDS.
3. Some drugs cause irritation to the gastric mucosa.
4. Patients cannot be dosed these formulations just before going to bed.
5. The dosage form must be taken with a full glass of water.[14]
6. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
7. These systems also require the presence of food to delay their gastric emptying.[15]

VARIOUS APPROACHES TO GASTRIC RETENTION:

1. High density (sinking) systems or non floating delivery
2. Low density systems or Floating delivery
3. Mucoadhesive/Bioadhesive Systems
4. Expandable Systems
5. Superporous Hydrogel Systems
6. Magnetic Systems[16]

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS (GRDDS):

A) Effervescent FDDS
(I) Gas generating system
(II) Volatile liquid containing system
(B) Non- Effervescent FDDS
(I) Colloidal gel barrier system
(II) Microporous compartment system
(III) Floating microsphere
(IV) Alginate floating beads
(C) Raft forming system.

(A) Effervescent System FDDS:

These are matrix type of system. Prepared with the help of swellable polymer such as Methylcellulose and Chitosan and various effervescent compounds. Ex: sodium bicarbonate, tartaric acid, citric acid. These are formulated in such a way that when they come in contact with gastric content, $CO_2$is liberated and gets entrapped in swollen hydrocolloid which provides buoyancy to dosage form. The design of delivery system was based on swellable asymmetric triple layer tablet approach.

(I) Gas Generating Systems –These are low density FDDS is based on the formation of CO_2 within the device following contact with body fluids. The materials are fabricated so that upon arrival in stomach, $CO_2$is librated by acidity of the gastric content and is entrapped in the gellified hydrocolloid this produce upward motion of the dosage form and maintain its buoyancy.Decrease in specific gravity cause dosage form to float on the chime. The CO_2 generating components may be intimately mixed within the tablet matrix in which case a single layer or bilayered is produced which contain the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for a sustained release effect.

(II) Volatile liquid containing systems (Osmotically Controlled DDS) – As an Osmotically controlled floating system, the devicecomprised of a hallow deformable unit that was convertiblefrom a collapsed position after an extended period of time.A housing was attached to the deformable unit and it wasinternally divided into a first and second chamber with thechambers separated by an impermeable, pressure responsive movable bladder. The first chamber contain an active drug , while the second chamber contain a volatile liquid, such as cyclopentane or ether that vaporizes at physiological temperature to produce a gas, enabling the drug reservoir to float. To enable the unit to exit from the stomach, the device contained a bio-erodible plug that allowed the vapors to escape.

B) Non-Effervescent FDDS:-

Non-Effervescent FDDS use a gel forming (or) swellable cellulose type of hydrocolloids, Polysaccharide, matrix forming polymer like polycarbonate, polymethacrylate and polystyrene. One of the formulation methods involves the mixing of the drug with gel forming hydrocolloids which swell in contact with gastric fluid after oral administration and maintains integrity of shape and a bulk density barrier, the air trapped by swollen polymer confer buoyancy to the dosage forms.[17]

(I) Colloidal gel barrier system:

Hydrodynamically balanced system (HBS), which containsdrugs with gel forming hydrocolloids, was first designed bySheth and Tossounian in 1975. These systems incorporate ahigh level (20-

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75%w/w) of one or more gel forming, highly swellable, cellulose type hydrocolloids, polysaccharides and matrix forming polymers. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug.

(II) Microporous compartment system: This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug.[18]

(III) Floating microsphere: Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods . The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. 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. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours.[19]

(IV) Alginate floating beads: Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence, time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hour.[15]

(C) Raft forming system: Raft forming system have received much attention for thedelivery of antacid and drug Delivery for gastro infectionand disorders on contact with gastric fluid a gel formingSolution swells and forms a viscous cohesive gel containingentrapped CO_2bubbles. Which Forms raft layer on top ofgastric fluid which releases drug slowly in stomach. Often used for gastro esophageal reflux treatment.[17]

Table No.1: Ingredient Used For Increasing GRT.[20]

Polymers And Other Ingredients	Example
Hydrocolloids (20%-75%)	Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite®), Sodium CMC, MC, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, , CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbo-nate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15
Inert fatty materials (5%-75%)	Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.
Effervescent agents	Sodium bicarbonate, citric acid, tartaric acid, DiSGC (Di-Sodium Glycine Carbonate), CG (Citroglycine).
Release rate accelerants (5%60%)	Lactose, Mannitol
Release rate retardants (5%-60%)	Dicalcium phosphate, Talc, Magnesium stearate

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Buoyancy increasing agents (upto80%)	Ethyl cellulose
Low density material	Polypropylene foam powder (Accurel MP 1000®).

Table 2 : Conventional v/s Gastroretentive drug delivery system[21]

Sr. No.	Conventional drug delivery system	Gastroretentive drug delivery system
1	High risk of toxicity	Very low risk of toxicity
2	Less patient compliance	Improves patient compliance
3	Not suitable for delivery of drugs with narrow absorption window in small intestinal region.	Suitable for delivery of drugs with narrow absorption window in small intestinal region.
4	Not much advantageous for Drugs having rapid absorption through GIT	Very much advantageous for Drugs acting locally in the stomach
5	Drugs which are poorly soluble at an alkaline pH	Drugs having rapid absorption through GIT
6	No risk of dose dumping.	Possibility of dose dumping.

APPLICATIONS OF FDDS:

- **Enhanced Bioavailability:** The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDFCR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption [50]. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) & enteric coated LASIX-long product (29.5%)
- **Sustained Drug Delivery:** Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents. Hydrodynamically Balanced System type dosage forms remain in the stomach for several hours, increase the gastric residence

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time and thus release the drug over a prolonged period of time. Madopar HBS formulation has shown to release levodopa for up to 8 hour in vitro, whereas the standard formulation released levodopa in less than 30 minutes. These systems have a bulk density of e.g., Sustained release floating capsules of nicardipine hydrochloride were developed & 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)

- **Reduced Fluctuations of Drug Concentration:** The fluctuations in plasma drug concentration are minimized, & concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.
- **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. 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.
- **Enhanced First-pass Biotransformation:** In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (Cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input. Floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances e.g., antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides And Tetracyclines) are taken up only from very specific sites of the GI mucosa.[22]

II. CONCLUSION:

Reviews on floating drug delivery system suggest us…

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. 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. A novel floating controlled-release drug delivery system was formulated in an effort increase the gastric retention time of the dosage form and to control drug release. FDDS promises to be a potential approach for gastric retention. Though several approaches and techniques are developed for FDDS, research in this area is needed until an ideal system with applicability and industrial feasibility is developed. All these drug delivery systems have their own advantages and drawbacks. To design a successful GRDDS, it is necessary to take into consideration the physicochemical properties of the drug, physiological events in the GIT, formulation strategies, and correct combination of drug and excipients.

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