Review Article

Floating Drug Delivery System to Increase Gastric Retention of Drug: A Review

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ABSTRACT

Floating systems have the property of retaining the dosage units in the stomach for prolonged period of time and are useful for drugs acting locally in the gastro intestinal tract (GIT), drugs which are poorly soluble and unstable in intestinal fluids. Recently various efforts are being made to design systems such as Floating Drug delivery systems (FDDS), Swelling and Expanding Systems, Bioadhesive systems, Modified shape systems, High density systems etc. These systems are advantageous in improving GIT absorption of drug with controlled release due to specific site absorption limitations. The main objective of developing these systems is to increase the safety of a product to extend its duration of action and decrease side effects of drugs. These systems have more flexibility in dosage form design than conventional dosage form. Several approaches have recently been developed to extend gastrointestinal transit time by prolonging residence time of drug delivery system in the GIT.

Keywords: Floating drug delivery system, gastroretentive system, effervescent, non-effervescent.

1. INTRODUCTION

The oral route is the most preferable route of drug delivery due to the ease of administration, low cost of therapy, patient compliance and flexibility in formulation etc. Oral sustained drug delivery formulations show some limitations connected with the gastric emptying time. Variable and too rapid gastrointestinal transit could result in incomplete drug release from the device into the absorption window leading to diminished efficacy of the administered dose. It is evident from the recent research and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today[1].

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[2].

The relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem. Overall, the intimate contact of the DDS with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption[3,4]. These considerations have led to the development of a unique oral controlled release dosage form (CR-DF) with gastroretentive properties. After oral administration, such a dosage form would be retained in the stomach and release the drug there, in a controlled and prolonged manner, so that the drug could be supplied continuously from its absorption sites in the upper gastrointestinal tract[5]. Gastroretentive 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. It is also suitable for local drug delivery to the stomach and proximal small intestines[6]. Gastro retention helps to provide better availability of new products with suitable therapeutic activity

and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs of these drugs[7].

2. Basic gastrointestinal tract physiology

Stomach is an enlargement of GI tract is nearly J shaped organ (Fig 1). 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[8].

2.1 Stomach physiology

The stomach is an expanded section of the digestive tube between the esophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae[9]. There are images to four major types of secretary epithelial cells that cover the surface of the stomach and extend down into gastric pits and glands:

- Mucous cells: secrete alkaline mucus that protects the epithelium against shear stress and acid.
- Parietal cells or oxyntic cells: secrete hydrochloric acid.
- Chief cells or peptic cells: secrete pepsin, a proteolytic enzyme.
- G cells: secrete the hormone gastrin.

The contraction of gastric smooth muscle serves two basic functions

- Ingested food is crushed, ground, mixed and liquefying to form Chyme.
- Chyme is forced through the pyloric canal into the small intestine a process called gastric emptying.

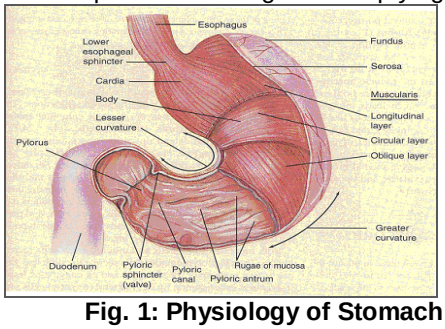

Fig. 1: Physiology of Stomach

2.2 Gastric motility

Gastric motility is controlled by a complex set of neural and hormonal signals. Nervous control originates from the enteric nervous system as well as parasympathetic (predominantly vagus nerve) and sympathetic systems. A large battery of hormones has been shown to influence gastric motility- for e.g. both gastrin and cholecystokinin act to relax the proximal stomach and enhance contractions in the distal stomach. The bottom line is that the patterns of gastric motility are as a result from smooth muscle cells integrating a large number of inhibitory and stimulatory signals. Liquid readily pass through the pylorus in spurts, but solids must be reduced to a diameter of less than 1-2 mm before passing pyloric gatekeeper. The gastric volume is important for dissolution of the dosage form *in vivo.* The resting volume of the stomach is 25-50 ml. There is a large difference in gastric secretion of normal and achlorhydric individuals. Gastric pH also has pronounced effect on absorption of drug from delivery system. The pH of fasting stomach is 1.2-.2.0 and in fed condition 2.0-6.0[10].

2.3 Gastric empty rate

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states.

2.3.1 Fasting state

During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours[11]. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington[12].

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 with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 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.

2.3.2 Fed state

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in Phase II of fasting state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate[13]. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

3. Floating drug delivery system (fdds) and mechanism of floating

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), mucoadhesive systems, low-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. 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 (Fig 2) 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 gastric residence time (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 retention, 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 floating. The object floats better if F is on the higher positive side[14]. 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

$F = F_{buoyancy} - F_{gravity} = (D_f - D_s)\, gv$

Where, F= total vertical force, D_f = fluid density,

D_s = object density, v = volume and g = acceleration due to gravity.

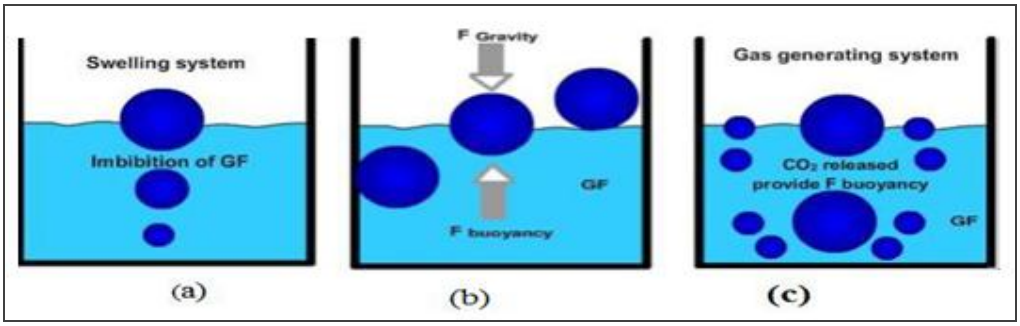

Fig. 2: Mechanism of Floating System, GF=Gastric fluid.

4. Advantages of floating drug delivery system

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery[15]. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Site-specific drug delivery.
8. FDDS improves patient compliance by decreasing dosing frequency.

9. Better therapeutic effect of short half-life drugs can be achieved.
10. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.

5. Disadvantages of floating drug delivery system[1]

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float Some drugs present in the floating system causes irritation to gastric mucosa.
3. Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.

Approaches to design floating drug delivery systems

The following types of dosage forms have been used for the design of floating dosage forms of single- and multiple-unit systems.

6.1 Low density approach for single unit dosage forms

In low-density approach, the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells, popcorn, poprice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethylcellulose or hydroxypropyl cellulose depending on the 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 into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behavior. The device is of swallowable size, remains afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated.

Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time, the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. The success of HBS capsule as a better system is best exemplified with chlordiazeopoxide hydrochloride. The drug is a classical example of a solubility problem wherein it exhibits a 4000-fold difference in solubility going from pH 3 to 6 (the solubility of chlordiazepoxide hydrochloride is 150 mg/mL at acidic pH and is ~0.1 mg/mL at neutral pH). HBS of chlordiazeopoxide hydrochloride had comparable blood level time profile as of three 10-mg commercial capsules. HBS can either be formulated as a floating tablet or capsule. Many polymers and polymer combinations with wet granulation as a manufacturing technique have been explored to yield floatable tablets.

Various types of tablets (bilayered and matrix) formulated with low density polymers, have shown to have floatable characteristics. Some of the polymers used are hydroxypropyl cellulose, hydroxypropyl methylcellulose, crosspovidone, sodium carboxymethyl cellulose and ethyl cellulose. Self-correcting floatable asymmetric configuration drug delivery system employs a disproportionate 3-layer matrix technology to control drug release[16]. The 3-layer principle has been improved by development of an asymmetric configuration drug delivery system in order to modulate the release extent and achieve zero-order release kinetics by initially maintaining a constant area at the diffusing front with subsequent dissolution/erosion toward the

completion of the release process. The system was designed in such a manner that it floated to prolong gastric residence time *in vivo*, resulting in longer total transit time within the gastrointestinal tract environment with maximum absorptive capacity and consequently greater bioavailability. This particular characteristic would be applicable to drugs that have pH-dependent solubility, a narrow window of absorption, and are absorbed by active transport from either the proximal or distal portion of the small intestine [17].

Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation[18].

6.2 Multiple-unit dosage forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkyl cyanoacrylate. Spherical polymeric microsponges, also referred to as “microballoons,” have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent *in vitro* floatability [18]. In carbon dioxide–generating multiple-unit oral formulations several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature[19].

6.3 Advantage of multiple system[20]

Multiple unit formulations show a more predictable release profile and less significant impairing of performance due to failure of units. Multiple systems allow co-administration of units with different release profiles or containing incompatible substances. Multiple system permit a larger margin of safety against dosage form failure compared with single-unit dosage forms.

7. Criteria for selection of drug candidate for fdds

7.1 Desirable half-life

The half-life of a drug is an index of its residence time in the body. If the drug has a short half life of less than 2 hours, the dosage form may contain a prohibitively large quantity of the drug.

7.2 High therapeutic index.

Drugs with low therapeutic index are not suitable for incorporation in controlled release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities e.g Digitoxin.

7.3 Small dose

If the dose of a drug in the conventional dosage form is recommended dose, its suitability as a candidate for FDDS is seriously undermined. This is chiefly because the size of a unit dose FDDS formulation would become too big, to administer without difficulty.

7.4 Aqueous solubility

Absorption of poorly water-soluble drugs is often dissolution rate limited. Such drugs do not require any further control over their dissolution rate and thus may not seem to be good candidates for oral controlled release formulations. FDDS formulations of such drugs may be aimed at making their dissolution more uniform rather than reducing it. Drugs with aqueous solubility make good candidates for FDDS dosage form.

7.5 G.I absorption

The absorption of the drug candidate from the gastrointestinal tract is dictated by the location of the dosage form in the gastrointestinal tract and the GI contents. Some drugs are more efficiently absorbed from the upper part of GI tract while others are absorbed from the lower part of GI tract. In such cases where the drug has a particular absorption site in the GI tract (i.e. Absorption window), stomach or upper part of the small intestine for example, the drug may not be completely absorbed when administered in the form of a typical controlled drug delivery system. It is clear that for such drugs having an “absorption window” as stomach or upper part of small intestine, an effective oral controlled drug delivery system should be designed not only to deliver drug at a controlled rate, but also to retain the drug in the upper part of the gastrointestinal tract for a long period of time.

7.6 Stability to wide pH range, G.I enzymes and flora

Stability of the drug in the GI contents is important to ensure a complete and reproducible drug input into the body. Typically the drug must be stable in the pH range of 1 to 5 [7,21].

8. (A) **Potential drug candidates for gastroretentive drug delivery systems**

The following types of drug are suitable candidates for GRDDS given in (Table 1)

1. Drugs those are locally active in the stomach e.g. misroprostol, 5-flurouracil, antacids etc.
2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. Atenolol, L-DOPA, para aminobenzoic acid, furosemide, riboflavin etc.
3. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
4. Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
5. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.
6.

A List of marketed products of GRDDS are given in (Table 2).

8. **(B) Drugs unsuitable for gastroretentive drug delivery systems**

1. Drugs that have very limited acid solubility e.g. phenytoin etc.
2. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
3. Drugs intended for selective release in the colon e.g. 5-amino salicylic acid and corticosteroids etc.[22].

Table 1: List of drugs formulated as single and multiple unit forms of floating drug delivery systems[23]

Dosage form	Drugs
Tablets	Cholrpheniramine maleate, Theophylline, Furosemide, Ciprofloxacin, Captopril, Acetylsalicylic acid, Nimodipine, Amoxycillin trihydrate, Verapamil HCl, Isosorbide dinitrate, Sotalol, Isosorbide mononitrate, Acetaminophen, Ampicillin, Cinnarazine, Diltiazem, Florouracil, Piretanide, Prednisolone, Riboflavin- 5`Phosphate.
Capsules	Nicardipine, L-Dopa and benserazide, chlordizepoxide HCl, Furosemide, Misoprostol, Diazepam,Propranlol, Urodeoxycholic acid.
Microspheres	Verapamil, Aspirin, Griseofulvin, p-nitroanilline, Ketoprofen, Tranilast, Ibuprofen, Terfenadine
Granules	Indomethacin, Diclofenac sodium, Prednisolone
Films	Cinnarizine
Powders	Several basic drugs.

Table 2: Generally manufactured marketed product[24, 25]

S.No	Brand name	Drug (dose)	Company, Country	Remarks
1	Modapar®	Levodopa (100 mg), Benserazide (25 mg)	Roche Products, USA	Floating CR capsule
2	Valrelease®	Diazepam(15 mg)	Hoffmann LaRoche, USA	Floating capsule
3	Liquid Gavison®	Al hydroxide (95mg), Mgcarbonate(358mg)	Glaxo Smith Kline, India	Effervescent floating liquid alginate preparation
4	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
5	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
6	Cifran OD®	Ciprofloxacin (1 gm)	Ranbaxy, India	Gas generating Floating tablet
7	Cytotec®	Misoprostal (100 mcg/200mcg)	Pharmacia, USA	Bilayer floating capsule
8	Oflin OD®	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet

9. Types of floating drug delivery systems

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

A. Effervescent System, and

B. Non- Effervescent System.

9.1 Effervescent system

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making

it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types.

I. Gas Generating Systems

II. Volatile Liquid/Vacuum Containing Systems.

9.1.1. Gas generating systems

1. Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

These are formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet (Fig 3). These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. 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.

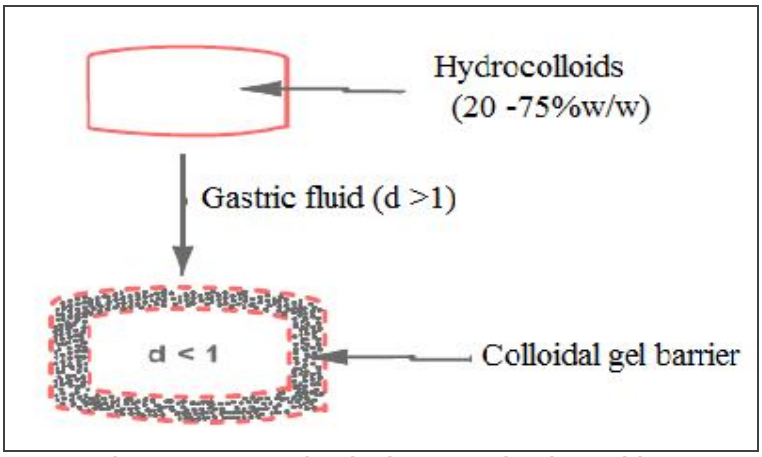

Fig. 3: Intra Gastric Single Layer Floating Tablet

2. Intra Gastric Bilayer Floating Tablets

These are also compressed tablet and containing two layer (Fig 4) i.e.,

i. Immediate release layer and

ii. Sustained release layer.

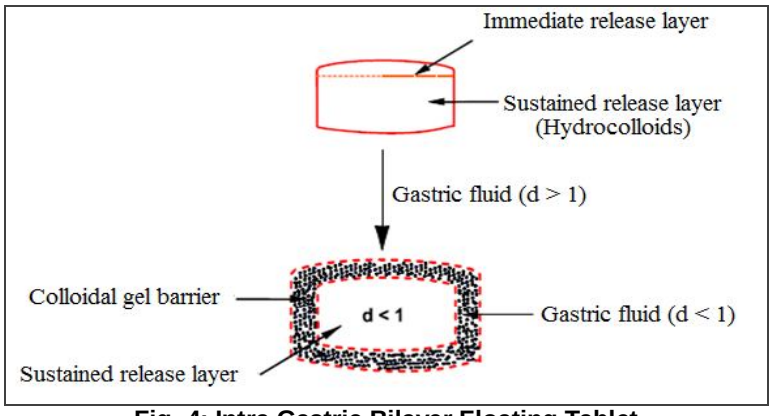

Fig. 4: Intra Gastric Bilayer Floating Tablet

3. Multiple Unit type floating pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers (Fig 5). The inner layer consists of effervescent agents while the outer layer is of swellable membrane

layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system.

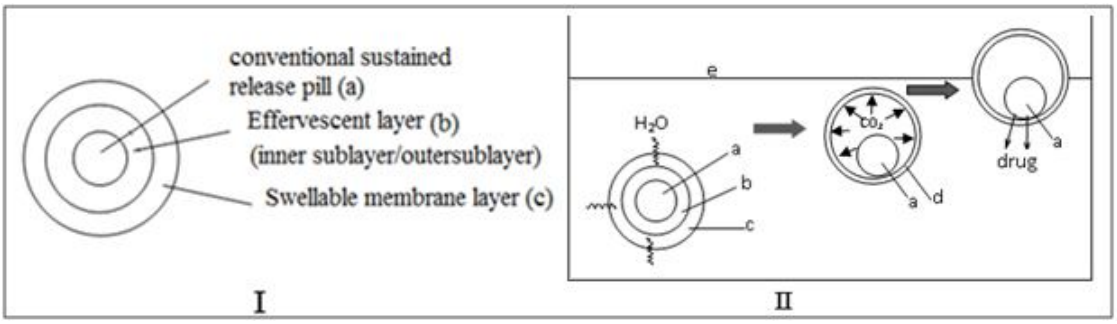

Fig. 5: (I) A multi-unit oral floating dosage system.
(II) Stages of floating mechanism: (A) penetration of water;
(B) generation of CO_2 and floating; (C) dissolution of drug.
Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C).

9.1.2. Volatile Liquid / Vacuum Containing Systems

1. Intragastric Floating Gastrointestinal Drug Delivery System

These system can be made to float in the stomach because of floatation chamber, which may be a
vacum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microprous compartment, (Fig 6).

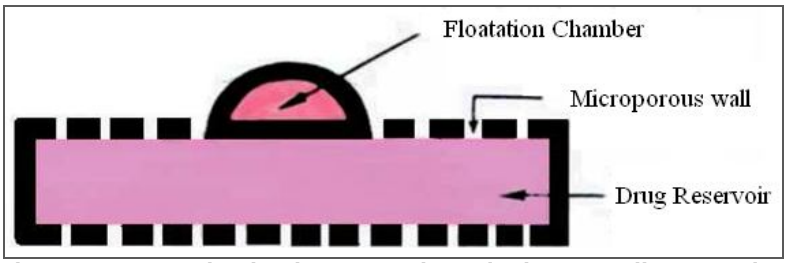

Fig. 6: Intra Gastric Floating Gastrointestinal Drug Delivery Device

2. Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach (Fig 7). These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.

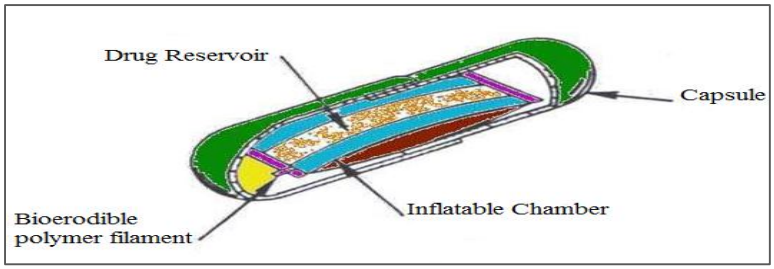

Fig. 7: Inflatable Gastrointestinal Delivery System

3. Intragastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule (Fig 8). In the stomach, the capsule quickly disintegrates to release the intragastirc osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

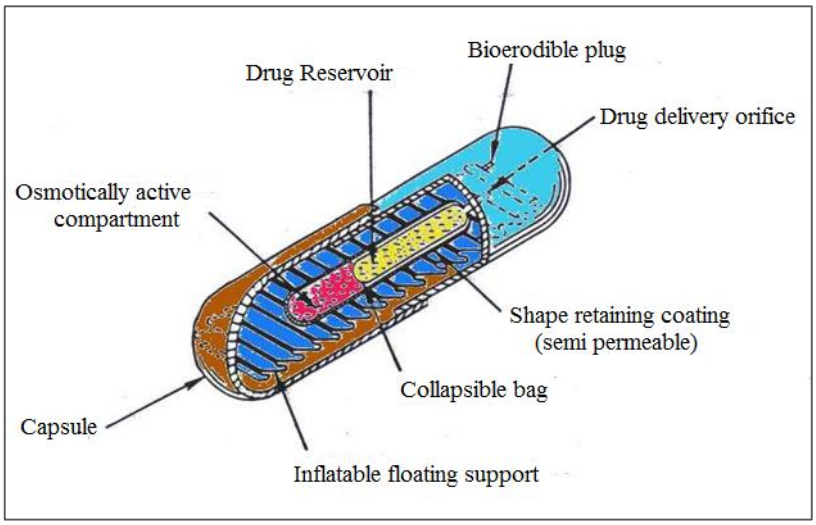

Fig. 8: Intragastric Osmotically Controlled Drug Delivery System

11.2 Non effervescent systems

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as chitosan and carbopol. Various types of this system are:

1. Single Layer Floating Tablets

These are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2. Bilayer Floating Tablets

A bilayer tablet contain two layers; one immediate release layers which release initial dose from system while the another sustained release layer absorbs 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.

3. Alginate 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, these floating beads gave a prolonged residence time of more than 5.5 hour.

4. Hollow Microspheres
Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The drug and polymer dissolved in ethanol:dichloromethane to form clear solution. This clear solution was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*[19].

10. Factors affecting gastric retention
There are several factors that can affect gastric emptying (and hence GRT) of an oral dosage form. These factors are as follows.

1. Density
GRT is a function of dosage form buoyancy that is dependent on the density. A buoyant dosage form having a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

2. Size
Dosage form units with a diameter of less than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm[19].

3. Shape of dosage form
Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have better GRT ≈ 90-100% retention at 24 hours compared with other shapes[23].

4. Single or multiple unit formulation
Multiple unit formulations show a more predictable release profile and less significant impairing of performance due to failure of units. Multiple systems allow co-administration of units with different release profiles or containing incompatible substances. Multiple system permit a larger margin of safety against dosage form failure compared with single-unit dosage forms[23].

5. Fed or unfed state
Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myloelectric cycle (MMC) that occurs every 1.5-2 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.

6. 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.

7. Caloric content
GRT can be increased by 4-10 hours with a meal that is high in proteins and fats.

8. Frequency of feed
GRT can increase by over 400 minutes when successive meals are given, compared with a single meal due to the low frequency of MMC.

9. Gender
Mean ambulatory GRT in males (3.4 ± 0.6 hours) is lesser compared with their age- and race-matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.

10. Age
Elderly people, especially those over 70, have a significantly longer GRT.

11. Posture
Gastric emptying is favored while standing and lying on the right side since the normal curvature of the stomach provides a downhill path, whereas lying on the left side or in supine position retards it.

12. Disease states
Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying, while partial or total gastrectomy, duodenal ulcer and hyperthyroidism promote it.

13. Concomitant drug administration
Drugs that retard gastric emptying include poorly soluble antacids (aluminum hydroxide), anticholinergics (atropine, propantheline), narcotic analgesics (morphine) and drugs such as tricyclic antidepressants (imipramine, amitriptyline), metoclopramide, domperidone, cisapride stimulate gastric emptying[1 26,27,28, 29].

11. Applications of FDDS
1. Enhanced bioavailability
The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR 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.

2. Sustained drug delivery
Oral CR formulations are encountered with problems such as less 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. These systems are relatively larger in size and passing from the pyloric opening is prohibited.

3. Site specific drug delivery systems
These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine. Controlled, slow delivery of drug meant for local action in stomach to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency. Eg: Furosemide and Riboflavin.

4. Absorption enhancement
Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.

5. Minimized adverse activity at the colon
Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

6. Reduced fluctuations of drug concentration
Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the conventional release dosage forms. Thus, fluctuations in drug concentration are minimized and 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[30].

12. Evaluation of floating drug delivery system
Evaluation of FDDS is performed to assess the physicochemical properties and release characteristics of the formulations.

12.1 in-vitro Evaluation
1) Buoyancy / floating test
The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

2) Swelling study
The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. Water uptake was measured in terms of percent weight gain, as given by the equation [22].

$$W_U = \frac{W_t - W_0}{W_0} \times 100$$

W_U = Percentage water uptake
W_t = Weight of dosage form at time t.
W_0 = Initial weight of dosage form
The dimensional changes can be measured in terms of the increase in tablet diameter and/or thickness over time[23].

3) Magnetic Resonance Imaging
Magnetic resonance imaging (MRI) is a noninvasive technique that is not associated with radioactivity and allows observation of the total anatomical structure in relatively high resolution. The visualization of the GI tract by MRI has to be further improved by the administration of contrast media. For solid

DFs, the incorporation of a superparamagnetic compound such as ferrous oxide enables their visualization by MRI. The technique is safe and allows obtaining many pictures from the same subject.

4) Radiology (X-Ray)

In this technique, a radio-opaque material has to be incorporated in the DF, and its location is tracked by X-ray pictures. The technique is used to evaluate gastroretentivity of GRDFs and the disintegration rate of DFs in vivo, and also to determine the esophageal transit. Although it is considered cheap and a simple method to use, its major disadvantage is the safety issue owing to repeated exposure to X-ray that increase the risk for the volunteers[31].

12.2 In-vivo Evaluation

1) in vivo buoyancy

Jain, Agarwal and Jain (2006a) have studied studied the gastric retention time of floating microspheres by gamma scintigraphy. The *in vivo* transit behavior of the floating and non floating microspheres was monitored using 12 one-year-old male albino rabbits. These rabbits were divided into two groups, i.e., group I and group II.

In order to standardize the conditions of GI motility, the animals were fasted for 12 hours prior to the commencement of each experiment. Floating microspheres (100 mg) were orally administered in suspension form to the animals in group I and non-floating microspheres were administered to group II, followed by a sufficient volume of drinking water. The location of the formulation in the stomach was monitored by keeping the subjects in front of a gamma camera. In between the gamma scannings, the animals were freed and allowed to move and carry out normal activities, but were not allowed to ingest any food or water until the formulation had emptied the stomach completely.

Kawashima *et al.* (1991) prepared hollow microspheres made with Eudragit S, containing barium sulfate as a contrast agent for the radiographical *in vivo* test. The study was carried out with two healthy male volunteers, free of detectable gastrointestinal diseases or disorders. Each subject, having fasted overnight, had a light Japanese breakfast (one rice ball and one cup of soup). After 30 minutes, each subject ingested two hard-gelatin capsules packed with hollow microspheres (1000 mg), together with 100 ml of water. The intragastric behavior of the hollow microspheres after dosing was observed by taking a series of X-ray photographs at suitable intervals. Cui *et al*. (2008) and Sato *et al*. (2004a) had performed the same study on healthy human volunteers, using gamma scintigraphy[32].

13. CONCLUSION

Gastroretentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery designing controlled release systems for better absorption and enhanced bioavailability.Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms.

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