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FLOATING DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
The recent scientific and patented literature concluded that an increased interest in novel dosage forms which retained in the stomach for prolong and predictable period of time has been shown. Various technological attempts have been made in the research and development of rate-controlled oral drug delivery systems to overcome physiological diversities, as short gastric residence times and unpredictable gastric emptying times using gastro retentive drug delivery system. It is a well known fact that differences in gastric physiology, such as, gastric pH and motility exhibit both intra as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behavior. Various attempts have been made to develop Gastro retentive delivery systems. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems, swelling and expanding systems, polymeric bio adhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. Floating dosage forms are emerging as a promising dosage forms. Floating dosage form can be prepared as tablets, capsules by adding suitable ingredients as well as by adding gas generating agent. In this review various techniques used in floating dosage forms along with current & recent developments of stomach specific floating drug delivery system for gastro retention are discussed.
Keywords: Floating Drug Delivery System, Drug Delivery System, Gastro Retentive Floating Dosage Forms, Floating Dosage Form, Gastric Residence Time

INTRODUCTION

Development of new drug molecule is expensive and time consuming. Improving safety efficacy ratio of old drugs has been attempted using different methods such as individualizing drug therapy, dose titration and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery, targeted delivery are other very attractive methods and have been pursued very vigorously.[9] Oral rout is the most convenient and extensively used for drug administration. This route has high patient acceptability, primarily due to ease of administration[8]. The aim of any drug delivery system is to afford a therapeutic amount of drug to the proper site in the body to attain promptly, and then maintain the desired drug concentration [10]. Oral drug delivery has been known for decades as the most widely used route of administration among all the routes that have been explored for the systemic delivery. All controlled release systems have limited applications if the systems cannot remain in the vicinity of the absorption site. The controlled release drug delivery system possessing the ability of being retained in the stomach is called gastro retentive drug delivery system. They can help in optimizing the oral controlled delivery of drugs having "absorption window" continually releasing the drug prior to absorption window for prolonged period of time, thus ensuring optimal bioavailability[7]A floating dosage unit is useful for drugs acting locally in the proximal gastrointestinal tract. These systems are also useful for drugs that are poorly soluble or unstable in intestinal fluids. Floating tablets and floating capsules are common examples of floating system [11].

GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

Drug candidates having 'absorption window' in a particular region of GI tract are difficult to be designed as oral controlled release drug delivery system (CRDDS). This is because only the drug released in the region preceding the 'window' and vicinity of 'absorption window' is available for absorption. Drug released from the CRDDS after the 'absorption window' has been crossed goes waste with no or negligible absorption occurring. The CRDDS possessing the ability of being retained in the stomach are called gastro retentive drug delivery systems (GRDDS) and they can help in optimizing the oral controlled delivery of drugs having 'absorption window' by continuously releasing drug prior to absorption window for prolong period of time thus ensuring optimal bioavailability[8]. Different types of gastro retentive drug delivery systems (GRDDS) are shown in Figure 1[3]

Gastro-retentive technologies

1. Low density system providing sufficient buoyancy to float over the gastric contents; floating drug delivery system (FDDS).
2. Swelling and expanding system in the gastric environment preventing transit from the gastric sphincter; Swelling system.
3. Bio adhesive system enabling the localized retention of the system in the stomach; Bio/ muco adhesive system.
4. High density systems sedimenting to the folds of stomach; high density system.[8]

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum. 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. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the inter digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington as shown in Figure 2

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (pre burst phase) lasts for 40 to 60 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]

Factors affecting gastric retention time

There are number of factors that affect the gastric retention time (GRT).

1. **Density** – GRT is a function of dosage form buoyancy that is dependent on the density.
2. **Size** – dosage form units with a diameter of more than 7.5mm

are reported to have an increased GRT compared with those with a diameter of 9.9mm.

3. **Shape of dosage form** – Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT ≈90% to 100% retention at 24 hours compared with other shapes.

4. **Single or multiple unit formulation** – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

5. **Fed or unfed state** – Under fasting conditions, the GI motility is characterised by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs 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.

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 to 10 hours with a meal that is high in proteins and fats.

8. **Frequency of feed** – The 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 less 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** – GRT can vary between supine and upright ambulatory states of the patient.

12. **Concomitant drug administration** – Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride affect GRT.

13. **Biological factors** – diabetes and Crohn's disease, etc affect GRT [6]

FLOATING DRUG DELIVERY SYSTEM

Floating system first described by Davis in 1968. "Floating systems or dynamically controlled systems are low-density systems that have sufficiently 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" [3]

Advantages of FDDS

1. **Enhanced bioavailability-** The bioavailability of some drugs (e.g. riboflavin and levodopa) CR-GRDF is significantly enhanced in comparison to administration of non- GRDF CR polymeric formulations.

2. **Enhanced first-pass biotransformation-** When the drug is presented to the metabolic enzymes (cytochrome P-450, in particular CYP-3A4) in a sustained manner, the presystemic metabolism of the tested compound may be considerably increased rather than by a bolus input.

3. **Sustained drug delivery/reduced frequency of dosing-** The drugs having short biological half life, a sustained and slow input from FDDS may results in a flip-flop pharmacokinetics and it reduced the dose frequency.

4. **Targeted therapy for local ailments in the upper GIT-** The prolonged and sustained administration of the drug from FDDS to the stomach may be useful for local therapy in the stomach.

5. **Reduced fluctuations of drug concentration-** The fluctuations in plasma 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.

6. **Improved receptor activation selectivity-** FDDS reduces the drug concentration fluctuation that makes it possible to obtained certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

7. **Reduced counter-activity of the body-** Slow release of the drug into the body minimizes the counter activity leading to higher drug efficiency.

8. **Extended time over critical (effective) concentration-** The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects.

9. **Minimized adverse activity at the colon -** Retention of the drug in GRDF at stomach minimize the amount of drugs that reaches the colon and hence prevent the degradation of drug.

10. **Site specific drug delivery-** A floating dosage form is a widely accepted approach especially for drugs which have limited absorption sites in upper small intestine [12]

Disadvantages of FDDS

1. Floating system is not feasible for those drugs that have solubility or stability problem in GIT.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water [13]
3. Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
4. Drugs which are irritant to Gastric mucosa are also not desirable or suitable.
5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the system.
6. The dosage form should be administered with a full glass of water (200-250 ml).
7. These systems do not offer significant advantages over the conventional dosage forms for drugs which absorbed throughout gastrointestinal tract [12]

CLASSIFICATION OF FDDS

1. Non-effervescent system
(a) Colloidal gel barrier system
(b) Micro porous compartment system
(c) Alginate beads
(d) Hollow microspheres

2. Effervescent system
(a) Volatile liquid containing systems
(b) Gas-generating systems

3. Non-effervescent system

(a)Colloidal gel barrier system- Hydro dynamically balanced system (HBS) was first designed by Sheth & Tossounian in 1975 such system contain drug with gel-forming hydrocolloids meant to remain buoyant on the stomach contents. This prolongs GI residence time and maximizes drug reaching its absorption site in the solution form hence is ready for absorption. These systems incorporate a high level (20-75% w/w) of one or more gel-forming, highly swell able, cellulose-type hydrocolloids [e.g. hydroxyethyl cellulose(HEC), hydroxypropyl cellulose (HPC), hydroxypropyle methyl cellulose (HPMC), sodium carboxymethyl cellulose (NaCMC)], polysaccharides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsules. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms 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, as shows in figure no 3.[12] As the exterior surface of the dosage form goes into the solution, the gel layer is maintained by the adjacent hydrocolloid layer becoming hydrated. The air trapped in by the swollen polymer maintains a density less than unity and confers buoyancy to these dosage forms.

The HBS must comply with three major criteria:

(1) It must have sufficient structure to form a cohesive gel barrier.

(2) It must maintain an overall specific density lower than of gastric contents.

(3) It should dissolve slowly enough to serve as a reservoir for the delivery system.

A bilayer tablet can also be prepared to contain one immediate-release and other sustained- release (SR) layer. Immediate-release layer delivers the initial dose, whereas SR layer absorbs gastric fluid and forms a colloidal gel barrier on its surface. This results in a system with bulk density lesser than that of the gastric fluid, and allow it remain buoyant in the stomach for an extended time period

(b)Microporous compartment system- This technology is based on the encapsulation of drug reservoir inside a microporous compartment with apertures along its top and bottom walls as shown in Figure 4[18]. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the un dissolved drug. In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through apertures, dissolves the drug, and carries the dissolved drug for continuous transport across the intestine for absorption [8]

(c)Alginate beads- Multiunit 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 a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate. The beads are separated, snap frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hrs. when compared with solid beads, which gave a short residence time of 1 hr, these floating beads gave a prolonged residence time of more than 5.5 hrs [8]

(d)Hollow microspheres

Hollow microspheres loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method as shown in Fig.5[14]. The ethanol:dichloromethane solution of the drug an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40ºC. the gas phase generated in dispersed polymer droplet by evaporating of dichloromethane formed an internal cavity in microsphere of polymer with drug. The micro balloons floated continuously over surface of acidic dissolution media containing surfactant for greater than 12 hrs in vitro. The drug released was high in pH 7.2 than in pH 6.8 [8]

Effervescent system:

A drug delivery system can be made to float in stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts.

(a) Volatile liquid containing system- The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, the gasifies at body temperature to cause the inflation of the chamber in the stomach. The devices are osmotically controlled floating systems containing a hollow deformable unit that can convert from a collapsed to an expanded position, and returns to collapsed position after an extended period. The deformable system consists of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains the drug and the second chamber contains volatile liquid .the device inflates, and the drug is continuously released from reservoir into the gastric fluid. The device may also consist of a bio erodible plug made up of PVA, polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach [8]

(b) Gas-generating system

These buoyant delivery system utilize effervescent reaction between carbonate/bicarbonate salts and citric /tartaric acid to liberate CO_2, which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chime as shown in Figure 6[16] . These tablets may be either single layered where in the CO_2 generating components are intimately mixed within the tablet matrix, or they may be bi layered in which the gas generating components are compressed in one hydrocolloid containing layer, and the drug in other layer formulated for a SR effect.

Multi-unit types of floating pills, which generates CO_2, have also been developed. The system consist of a SR pill as seed, surrounded by double layers. The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer is of a swell able membrane layer containing PVA, shellac, etc. Effervescent layer is divided into two sub-layer to avoid direct contact between sodium bicarbonate and tartaric acid. When the system is immersed in buffer solution at 37°C, swollen pills like balloons are formed having density less than 1 gm per ml. This occurs due to the CO_2 bi neutralization of the inner effervescent layer with the diffusion of water through the outer swell able membrane layer. These kinds of systems float completely within 10 minutes, and remain floating over extended periods of 5-6 hrs[8]

Drugs used in the formulation of stomach specific dosage forms

Floating microspheres: Aspirin, Griseofulvin, P-nitroaniline, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Tranilast and Terfinadine

Floating granules: Diclofenac sodium, Indomethacin and Prednisolone.

Films: Cinnarizine and Albendazole.

Floating tablets and pills: Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Fluorouracil, Cephalexin, Cefuroxime auxetil, Isosorbide mononitrate, paminobenzoic acid, Piretanide, Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol, pentoxyfilline and Diltiazem HCl, Iitopride HCl, Acyclovir, Cefuroxime axetil, Clarithromycin, 5-Fluorouracil.

Floating Capsules: Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin and Propranolol [12]

Drugs those are unsuitable for GRDDS

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 [14].

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), mucoadhesive 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 as shown in Figure 7[18]. 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, 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 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. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra gastric buoyancy capability variations.

$$F = F_{buoyancy} - F_{gravity}$$
$$= (D_f - D_s)\, gv \text{---} (1)$$

Where, F= total vertical force D_f = fluid density,
D_s = object density, v = volume and
g = acceleration due to gravity

APPROACHES TO DESIGN FLOATING DOSAGE FORMS

Floating drug delivery systems are among the several approaches that have been developed in order to increase the gastric residence time of the dosage forms [17]

Single-Unit Dosage Forms: In Low-density approach the globular shells apparently have 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. Hydro dynamically 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 a4000-fold difference in solubility going from pH 3 to 6 (the solubility of chlordiazepoxide hydrochloride is 150 mg/mL 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) have been shown to have floatable characteristics. Some of the polymers used are hydroxyl propyl cellulose, hydroxyl propyl methylcellulose, cross povidone, sodium carboxy methyl cellulose, and ethyl cellulose. Self-correcting floatable asymmetric configuration drug delivery system employs a disproportionate 3-layer matrix technology to control drug release. 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. 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.

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 above 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 polyalkylcyanoacrylate. 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. 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. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded [2]

FORMULATION OF FLOATING DOSAGE FORM

Following types of the ingredients can be incorporated in to floating dosage form

a. Hydrocolloids
b. Inert fatty materials
c. Release rate accelerants
d. Release rate retardant
e. Buoyancy increasing agents
f. Low density material
g. Miscellaneous

a. Hydrocolloids: Suitable hydrocolloids are synthethics, anionic or non ionic like hydrophilic gumes, modified cellulose derivatives. E.g. Accasia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2.Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy.

b. Inert fatty materials: Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and

hence increases the buoyancy. Example: Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and minaral oils can be used.

c. Release rate accelerants: The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5-60% by weight.

d. Release rate retardant: Insoluble substances such as dicalcium phosphate, talc, magnesium strearete decresesd the solubility and hence retard the release of medicaments.

e. Buoyancy increasing agents: Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80 % by weight.

f. Low density material: Polypropylene foam powder

g. Miscellaneous: Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporates in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems [15]

EVALUATION PARAMETERS OF FDDS

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro floating behavior show prolonged gastric residence in vivo. However, it has to be pointed out that good in vitro floating behavior alone is not sufficient proof for efficient gastric retention in vivo. The effects of the simultaneous presence of food and of the complex motility of the stomach are difficult to estimate. Obviously, only in vivo studies can provide definite proof that prolonged gastric residence is obtained.

Floating time: The test for floating time is usually performed in simulated gastric fluid or 0.1 mole.lit^{-1} HCl maintained at 37°C, by using USP dissolution apparatus containing 900 ml of 0.1 molar HCl as the dissolution medium. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time.

Drug release: Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

Drug loading, drug entrapment efficiency, particle size analysis, surface characterization(for floating microspheres and beads): Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. The particle size and the size distribution of beads or microspheres is determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM).

Measurement of buoyancy capabilities of the FDDS

The floating behaviour was evaluated with resultant weight measurements as shown in Figure 8[5]. The experiment was carried out in two different media like deionised water and simulated meal, in order to monitor possible difference. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behaviour and which was more in simulated meal medium compared to deionised water.

Content uniformity, Hardness, Friability (Tablets): These tests are performed as per described in specified monographs.

Resultant weight: The in vitro measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by force equivalent to the force F required to keep the object totally submerged in the fluid. This force determines the resultant weight of the object when immersed and may be used to quantify its floating or non floating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the Victoria sum of buoyancy (F_{buoy}) and gravity (F_{grav}) forces acting on the objects as shown in the equal

$F = F_{buoy} - F_{grav}$

$F = dfgV - dsgV = (df-ds)\ gv$

$F = (df - M/V)\ gV$

In which the F is total vertical force (resultant weight of the object), g is the acceleration due to gravity, df if the fluid density, ds is the object density is the object mass and V is the volume of the object.

VII. X-Ray/Gamma Scintigraphy: X-Ray/Gamma Scintigraphy is a very popularly used evaluation parameter for floating dosage form these days. It helps to locate dosage form in the GIT and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radio nucleide in a formulation allows indirect external observation using a γ-camera or scinti scanner.

VIII. Pharmacokinetic studies: Pharmacokinetic studies are the integral part of the in vivo studies. Sawicki et al studied the pharmacokinetics of Verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional Verapamil tablets of similar dose (40 mg). The t_{max} and AUC (0-infinity) values (3.75 h and 364.65 ng.ml^{-1}h respectively) for floating pellets were comparatively higher than those obtained for the conventional Verapamil tablets. (t_{max} value1.21 h, and AUC value 224.22 ng.ml-1h). No much difference was found between the C_{max} values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. The microspheres showed about 1.4 times more bioavailability, and the elimination half-life was increased by about three times than the free drug.

IX. Specific Gravity: Specific Gravity of the floating system can be determined by the displacement benzene as a displacing medium[15]

APPLICATIONS OF FDDS

Floating drug delivery system offers several applications for drugs having poor bioavailability because of the narrow absorption window in upper part of the gastrointestinal tract. It remains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

a) Sustained Drug Delivery: HBS (Hydrodynamic balance 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 formulation 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. Recently 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). Similarly a comparative study between the Madopar HBS and Madopar standard formulation was done and it was shown that the drug was released up to 8 hours in vitro in the former case and the release was essentially complete in less than 30 minutes in the latter case[4]

b) 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, eg, riboflavin and furosemide. 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 [1]

c) 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.

d) Enhanced bioavailability: The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There several different processes, related with absorption and transit of drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

e) 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 pro-vides the rationale for GRDF formulation for β-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

f) Reduced fluctuations of drug concentration: Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects 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 [3]

COMMERCIAL GASTRORETENTIVE FLOATING FORMULATIONS

Now a days a variety of marketed preparations of floating drug delivery system is available for various disease like antibiotics, antacids, sedatives, iron supplement. Some examples are in Table1[15]

FUTURE POTENTIAL OF FDDS

Floating dosage form offers various future potential as evident from several recent publications. Among the recently used clinical drugs several narrow absorption window drugs may benefit from compounding into a FDDS. Replacing parenteral administration of drugs to oral pharmacotherapy would substantially improve treatment. It may be believed that it can be possible with FDDS. Drugs that have poor bio-availability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently into FDDS. Thereby maximizing their absorption and improving their absolute bioavailability. The floating concept can also be utilized in the development of various anti-reflux formulations. Developing a controlled release system for the drugs, which are potential to treat the Parkinson's disease, is also an important area of consideration. Combination therapy to treat *H.pylori* infection in a single FDDS needs to be developed. The study of the effect of various geometric shapes in a more excessive manner than previous studies on gastro retentivity needs to be developed. The investigations can be concentrated on the concept of design of novel polymers according to clinical and pharmaceutical need [12]

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. The currently available polymer-mediated Non-effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. Number of commercial products and patents issued in this field are the evidence of it. 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. Some of the unresolved, critical issues like the quantitative efficiency of floating delivery systems in the fasted and fed states, role of buoyancy in enhancing GRT of FDDS and more than that formulation of an ideal dosage form to be given locally to eradicate *H.pylori,* responsible for gastric ulcers worldwide. With an increasing understanding of polymer behavior and the role of the biological factors mentioned above, it is suggested that future research work in the FDDS should be aimed at discovering means to control accurately the drug input rate into the GI tract for the optimization of the pharmacokinetic and toxicological profiles of medicinal agents. It seems that to formulate an efficient FDDS is sort of a challenge and the work will go on and on until an ideal approach with industrial applicability and feasibility arrives.

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Table 1 Marketed preparations of FDDS

Name	Company	Type and Drug	Remarks
MadoparHBS (PropalHBS)	Roche, USA	Floating capsule, Levodopa and benserazide	Floating CR capsules
Valrelease	Hoffman LaRoche, USA	Floating capsule, Diazepam	Floating Capsules
Topalkan	Pierre Fabre Drug, France	Floating Antacid, aluminum and magnesium mixture	Effervescent floating liquid alginate preparation
Conviron	Ranbaxy, India	Ferrous sulphate	Colloidal gel forming FDDS
Cifran	Ranbaxy, India	Ciprofloxacine (1 gm)	Gas generating floating form
Cytotech	Pharmacia, USA	Misoprostol (100 mcg/200 mcg)	Bilayer floating capsule

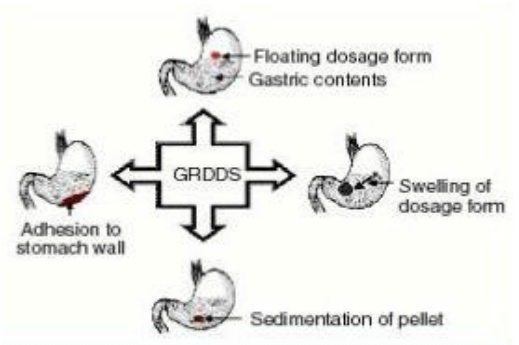

Figure 1- Types of gastro-retentive drug delivery system

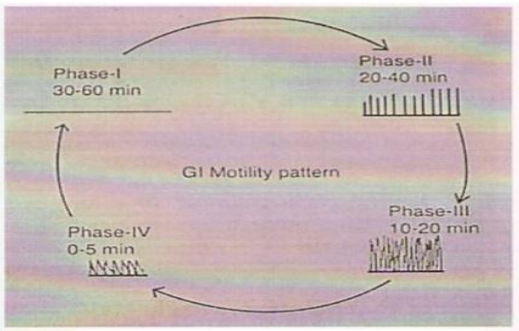

Figure 2- Gastrointestinal motility pattern

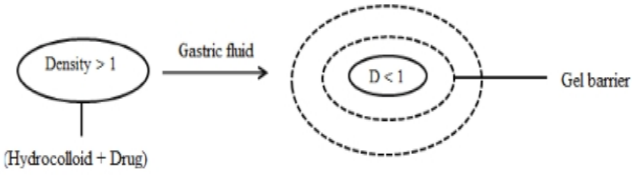

Figure 3- Colloidal gel barrier system

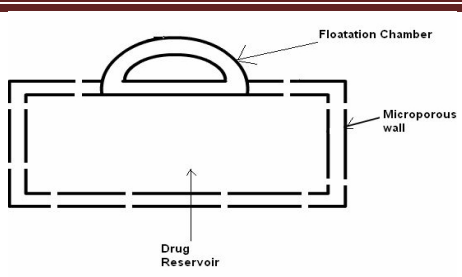

Figure 4- Microporous compartment system

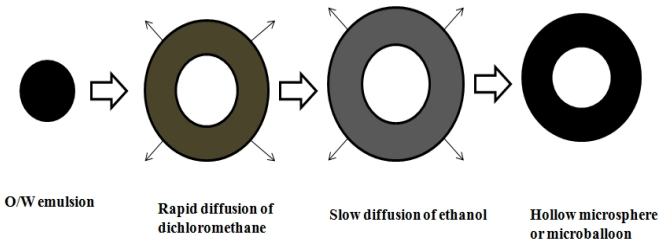

Figure 5- Hollow microspheres

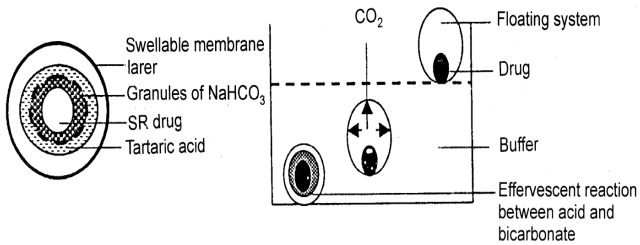

Figure 6- Gas-generating system

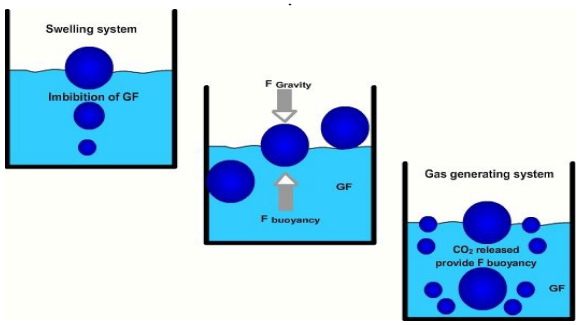

Figure 7- Mechanism of floating system

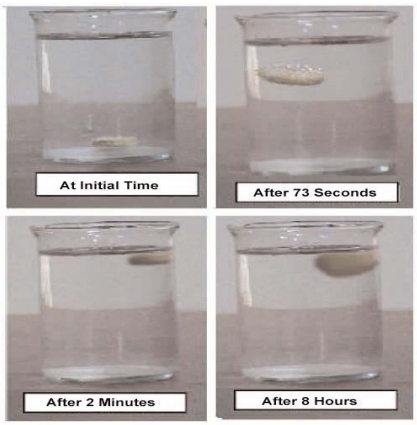

Figure 8- In vitro buoyancy study