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Overview On Floating Drug Delivery System

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ABSTRACT

The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The aim of writing this review on gastro retentive and floating drug delivery system was to compile the new literature with the principle mechanism of floatation to acquired gastric retention. The methodologies used in the development of FDDS by formulating effervescent and non effervescent floating tablets based on buoyancy mechanism. FDDS are of particular interest for drugs that are locally active and have narrow absorption window in stomach or upper small intestine, unstable in the intestinal or colonic environment, and exhibit low solubility at high pH values. This review article is in pursuit of giving detailed information on the pharmaceutical basis of their design, classification, advantages, *in vitro* evaluation parameters. Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. The recent developments of floating drug delivery systems (FDDS) including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems. 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 systems, mechanism, single unit, multiple units, evaluation Method.

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INTRODUCTION

Floating drug delivery systems (FDDS) are aimed to retain the drug in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. The principle is very simple i.e., to make the dosage form less dense than the gastric fluids so that it can float on them. Floating systems or Hydrodynamically 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. After release of drug, the residual system is emptied from the stomach. This result an increased gastric residence time and a better control of the fluctuations in plasma drug concentration. 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 [1].

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.[1]

Advantages of Floating Drug Delivery System [2,3]

Floating dosage systems are important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. 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. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
6. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be

available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

7. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
8. Treatment of gastrointestinal disorders such as gastro esophageal reflux.
9. Simple and conventional equipment for manufacture.
10. Ease of administration and better patient compliance.
11. Site-specific drug delivery.

Disadvantages of Floating Drug Delivery System

1. The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach [4].
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Some drugs present in the floating system causes irritation to gastric mucosa.
5. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.

Criteria Selection of Drug Candidate for FDDS

1. Absorption from upper GIT e.g. Ciprofloxacin.
2. Drugs having low pKa, which remains unionized in stomach for better absorption.
3. Drugs having reduced solubility at higher pH, e.g. Rosiglitazone maleate, captopril and chordiazepoxide.
4. Local action as it seen in the treatment of *Helicobacter pylori* by Amoxicillin.
5. 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.

6. To minimize gastric irritation this may be sudden increase of drug concentration in the stomach, e.g. NSAID.

Limitations of FDDS

1. The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.
2. The ability to float relies in the hydration state of the dosage form. In order to keep these tablets floating *In vivo*, intermittent administration of water (a tumbler full, every 2 hrs) is beneficial.
3. The ability of drug to remain in the stomach depends upon the subject being positioned upright.
4. FDDS are not suitable for the drugs that have solubility or stability problems in the gastric fluid.
5. Drug like Nifedipine is well absorbed along the entire GIT and undergoes significant first pass metabolism, but it is not a desirable candidate for FDDS since the slow gastric emptying may lead to the reduced systemic bio-availability.

Application of FDDS

1. Recent study indicated that the administration of diltiazem floating tablets twice a day might be more effective compared to normal tablets in controlling the blood pressure of hypertensive patients.
2. Modapar® HBS containing L-DOPA and Benserazide, here the drug was absorbed over a period of 6-8 hrs and maintained substantial plasma concentration for Parkinsonian patients. Cytotech® containing Misoprostol, a synthetic prostaglandin–EL analogue, for prevention of gastric ulcer caused by non-steroidal anti-inflammatory drugs (NSAIDS).[4]
3. 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.
4. FDDS also serves as an excellent drug delivery system for the eradication of *Helicobacter pylori*, which causes chronic gastritis and peptic ulcers.
5. Developing HBS dosage form for Tacrin provide better delivery systems and reduced its GI side effects.
6. Treatment of gastric and duodenal ulcer.[3]

APPROACHES TO DESIGN FLOATING DOSAGE FORMS

Several approaches were used to develop an ideal FDDS.These buoyant formulations include

hollow microsphere (micro ballons), granules, powders, tablets, pills, laminated film. Most of the floating systems reported in the literature are in dosage forms of single- and multiple-unit systems [5].

Single-Unit Dosage Forms:

In low density approaches[6],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[7], 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 ethyl cellulose or hydroxypropyl cellulose depending on the type of released 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[8]. Aperture or opening are present along the top and bottom walls through which the gastrointestinal fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains there in. 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 a float within the stomach for a prolong 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 prolong 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. 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 poly alkyl cyanoacrylate. Spherical polymeric micro sponges also referred to as "microballoons" have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability[9]. 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. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to18 mm in their expanded state is exceeded.

FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS

a) Formulation factors

i) Size of tablets

Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves [10].

ii) Floating and non-floating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units), were formulated and analyzed for their different properties. It was found that floating dosage units remained buoyant regardless of their sizes on the gastric contents throughout their residence in the gastrointestinal tract, while the nonfloating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the nonfloating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase [11].

iii) Density of tablets

Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density 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. A density of less than 1.0g/ml i.e. less than that of gastric contents has been reported. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities [12].

iv) Shape of tablets

The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, cloverleaf, string, pellet, and disk) were screened in vivo for their gastric

retention potential. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hrs [13].

v) Viscosity grade of polymer

Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity [14].

b) Idiosyncratic factors

i) Gender

Women have slower gastric emptying time than do men. Mean ambulatory GRT in meals (3.4±0.4 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 [15].

ii) Age

Low gastric emptying time is observed in elderly than do in younger subjects. Intra subject and inter subject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT [16].

iii) Posture

Upright position

An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size[13].Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by antral peristaltic movements [17].

Supine position

This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects [18].

iv) Concomitant intake of drugs

Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anti Cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of FDDS. The co

administration of GI-motility decreasing drugs can increase gastric emptying time [18].

v) Feeding regimen

Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. A GRT of 4-10 hrs has been reported after a meal of fats and proteins [19].

Mechanism of Floating Drug Delivery Systems (FDDS):

FDDS is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability [20]. This system is desirable for drugs with an absorption window in the stomach or in the upper small intestine [21]. This have a less density then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a 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 fluctuation in plasma drug concentration.

The major requirements for FDDS are [22]:

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).
- It must form a cohesive gel barrier.

The inherent low density can be provided by the entrapment of air (e.g. hollow chambers)[23] or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder) [24-26]. These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler [27]. The good floating behavior of systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the GIT which may produce irritation. On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce inter and intra- subject availabilities in drug absorption as well as to lower the possibility of dose dumping. Various multiple-unit floating system like air compartment multiple-unit system, hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method [28], micro particles based on low density foam powder[25], beads prepared by emulsion gelatin method etc [29] can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs.

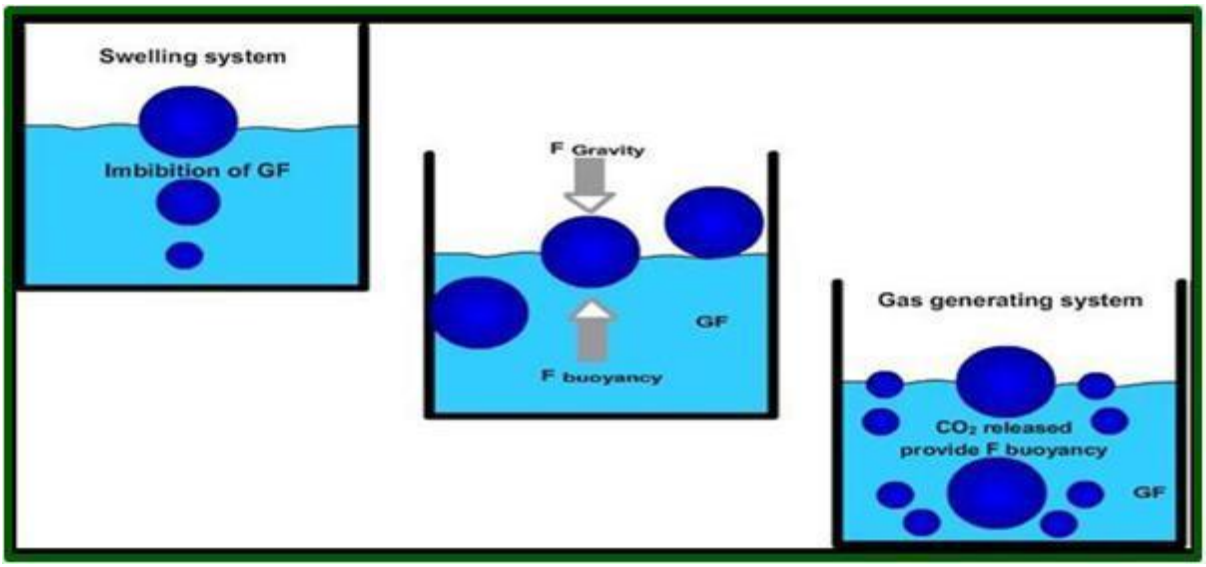

Figure 1: Mechanism of floating systems

CLASSIFICATION OF FDDS:

Based on the mechanism of buoyancy two distinctly different technologies **Effervescent Floating Drug Delivery System** and **Non- Effervescent Floating Drug Delivery System** has been utilized in the development of FDDS.

Effervescent Floating Drug Delivery System:

These floating systems are prepared with swellable polymers such as methocel or polysaccharides like chitiosan and effervescent component containing sodium bicarbonate, citric and/or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the jellified hydrocolloid. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate [30], multiple unit floating pills that generate CO_2 when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and poly vinyl pyrrolidone coated with hydroxyl propyl methyl cellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

a) Volatile liquid containing systems:

This type of system consists of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains the drug and the second chamber contains the volatile liquid. The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Poly vinyl alcohol, 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 systems from the stomach [31]. The device inflates, and the drug is continuously released from the reservoir into the gastric fluid.

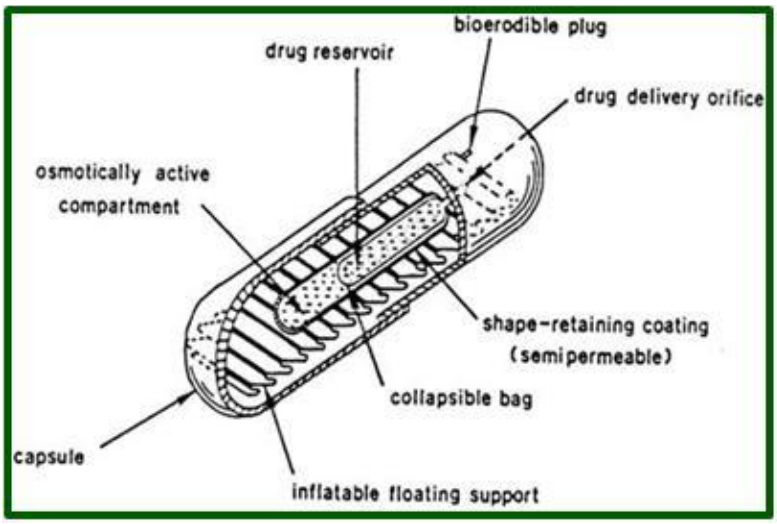

Figure 2: Volatile liquid containing system

b) Gas - generating systems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime [31,32]. These buoyant systems utilize matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid. The optimal stoicheometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1.

A new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into two sub layers to avoid direct contact between the two agents. These sub layers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the two effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml. It was found that the system had good floating ability independent of pH and viscosity and the drug (Para-amino benzoic acid) released in a sustained manner as shown in Figure: 3 [32].

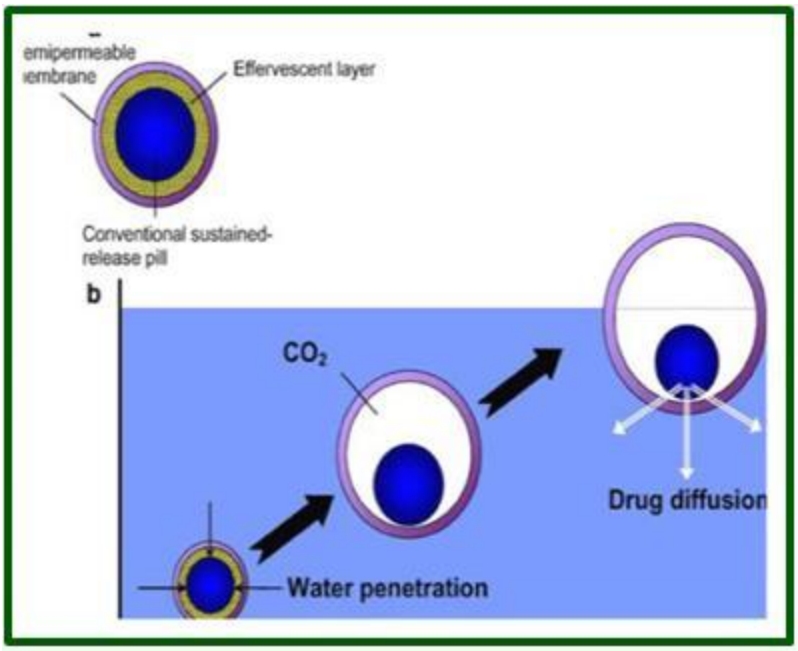

Figure 3: Principle mechanism of floating by CO_2 gas releasing method

Non- Effervescent Floating Drug Delivery System:

Non-effervescent FDDS are normally prepared from gel forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment [33]. The air entrapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include HPMC polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. The most commonly used excipient in non effervescent floating drug delivery system are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polyacrylate, polymethacrylate and polycarbonate. After oral administration these dosage form swells in contact with gastric fluid and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form.

This system can be further divided into the sub-types:

a. Hydrodynamically balanced systems OR Colloidal Gel Barrier System:

These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers [34]. HPMC, hydroxy ethyl cellulose,

hydroxyl propyl cellulose, sodium carboxy methylcellulose, polycarbophil, polyacrylate, polystyrene, agar, and carrageenans oralginic acid are used [35, 36].

The polymer is mixed with drugs and usually administered in HB-capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form[36]. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile. Several strategies have been tried and investigated to improve efficiencies of the floating hydro dynamically balanced system[36, 37].

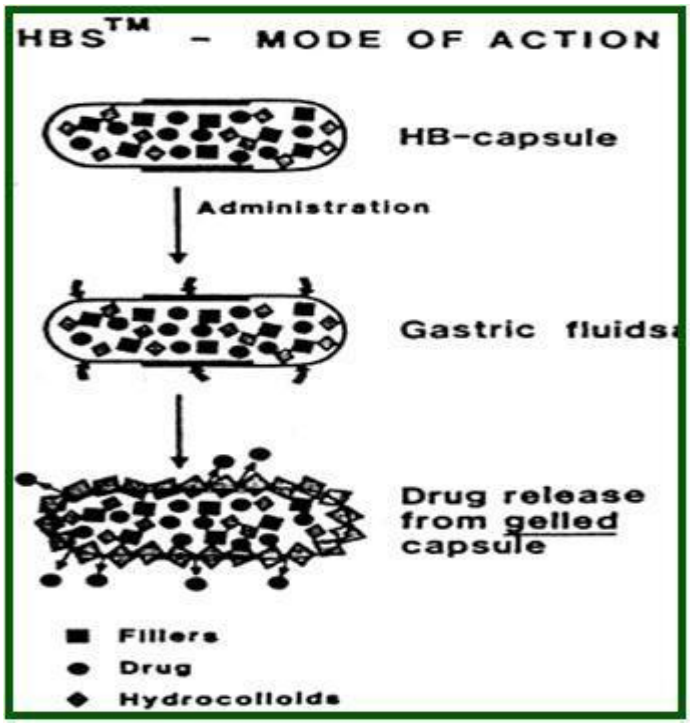

Figure 4: Working principle of hydrodynamically balanced system

b. Micro porous compartment system:

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the un-dissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption[38].

C. Hollow Microspheres:

Hollow microspheres are also known as microballoons. These microspheres are prepared by emulsion solvent diffusion method. In this method a solution or dispersion of drug and polymer is prepared in solvent (like dichloromethane, ethanol, isopropanol or a combination of these). This dispersion/solution is introduced into an aqueous solution of PVA (polyvinyl alcohol) forming an O/W type emulsion. This emulsion is agitated using propeller type agitator to remove the organic solvent, which produces the microballoons, size between 500-1000 mm.

Hollow microspheres with a drug loaded in their outer shells by an emulsion solvent diffusion method. The ethanol/dichloromethane solution of a drug and an enteric acrylic polymer was poured into an aqueous solution of PVA that was maintained at 40°C, with constant stirring. The gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in the microsphere of the polymer with drug.

The mechanism of formation of microsphere is reported, as ethanol a good solvent for acrylic polymer, preferentially diffuses out of dispersed droplets (organic phase) into an aqueous phase, the acrylic polymer instantly solidifies as a thin film at the interface between the aqueous phase and organic phase. It has also been reported that when the diffusion rate of solvent out of emulsion droplet was too slow, microspheres coalesced together. Conversely, when the diffusion rate of solvent was too fast, the solvent diffused into the aqueous phase before stable emulsion droplets could form, causing the aggregation of embryonic microsphere droplets.

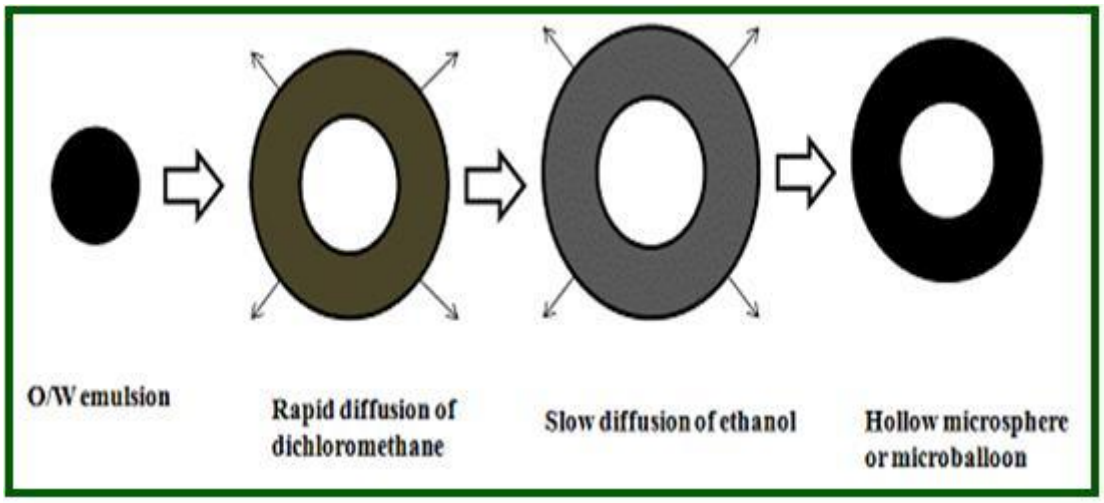

Figure 5: Formulation of floating hollow microsphere or microballoon

D. Alginate beads:

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium

alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hrs, leading to the formation of a porous system, which can maintain a floating force for over 12 hrs. These floating beads gave a prolonged residence time of more than 5.5 hrs[39].

Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. These microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hrs. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating[40].

PHARMACOKINETIC AND PHARMACODYNAMIC ASPECTS OF FDDS

The aim of this section is to delineate these aspects in order to suggest rational selection of drugs for which FDDS would be a beneficial strategy[41-44].

Pharmacokinetic aspects:

a) Absorption window:

The drug is within the category of narrow absorption window agents currently various experimental techniques are available that permit us to verify the absorption properties of the tested molecule, to determine the mechanism of intestinal absorption and to elucidate the permeability at different regions of the GI tract. In the case of absorption by active transporters that are capacity limited, the efficacy of the transport activity may increase following sustained presentation of the drug to the transporting enzymes in comparison to non-control release mode of administration.

b) Enhanced bioavailability:

Once it has been ascertained that the compound in question is defined as narrow absorption window, the possibility of improving bioavailability by continuous administration of the compound to the specific site should be tested. For example, we have found that certain bisphosphonates, including alendronate, are absorbed directly from the stomach. However, the magnitude of this pathway remains modest even in the case where the prolonged gastric retention of the bisphosphonate in rats is produced by experimental/surgical means. On the other hand, the bioavailability of control release (CR) floating systems of Riboflavin and Levodopa are significantly enhanced in comparison to administration of simple CR polymeric formulations. It may be concluded that several different processes, related to absorption and transit of the drug in

the gastrointestinal tract, act concomitantly and influence the magnitude of drug absorption. Therefore, in vivo studies are necessary to determine the release profile of the drug from the dosage form that will provide enhanced bioavailability[45].

c) Enhanced first pass biotransformation:

In a similar fashion to 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.

d) Improved bioavailability due to reduced P-glycoprotein (P-gp) activity in the duodenum:

In apparent contrast to the higher density of CYP3A4 at the upper part of the intestine, P-gp mRNA levels increase longitudinally along the intestine such that the highest levels are located in the colon. Therefore, for drugs that are P-gp substrate and do not undergo oxidative metabolism, such as Digoxin, floating systems may elevate absorption compared to the immediate and CR dosage forms.

e) Reduced frequency of dosing:

For drugs with relatively short biological half-life, sustained and slow input from control release floating system may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

f) Targeted therapy for local ailments in the upper GIT:

The prolonged and sustained administration of the drug from the floating systems to the stomach may be advantageous for local therapy in the stomach and the small intestine.

PHARMACODYNAMIC ASPECTS OF FDDS:

a) Reduced fluctuations of drug concentration:

Continuous input of the drug following floating system 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.

b) Improved selectivity in receptor activation:

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

c) Reduced counter-activity of the body:

In many cases, the pharmacological response, which intervenes with the natural physiologic processes, provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

d) Minimized adverse activity at the colon:

Retention of the drug in the GRDF 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 floating formulation for beta-lactam antibiotics that are absorbed only from the small intestine and presence in the colon leads to development of microorganisms [46].

Limitations of Floating Drug Delivery Systems

1. A high level of fluid in the stomach is required for drug delivery to float and work efficiently [47].
2. Drugs which have stability and solubility problems in GIT are not suitable candidates for these types of systems.
3. Drugs such as nifedipine, which under goes first pass metabolism may not be desirable for the preparation of these types of systems.
4. Not suitable for drugs that may cause gastric lesions e.g. Non- steroidal anti inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the GIT.
5. Drugs intended for selective release in the colon E.g. 5 - amino salicylic acid and corticosteroids etc.
6. The floating systems in patients with achlorhydria can be questionable in case of swellable system.
7. Retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.
8. The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.
9. Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique. Similarly retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.

10. In all the above systems the physical integrity of the system is very important and primary requirement.
11. The residence time in the stomach depends upon the digestive state. Hence FDDS should be administered after the meal [48].
12. The ability to float relies on the hydration state of the dosage form, In order to keep these tablets floating in vivo, intermittent administration of water (a tumbler full, every 2 hours) is beneficial[48].
13. The ability of the drug to remain in the stomach depends upon the subject being positioned upright[49].

Evaluation of Floating Drug Delivery System:

I. Pre-compression parameters like angle of Repose (θ)[50], Compressibility Index. bulk density, tapped density, Carr's index.

II. Post-compression parameters:

Shape of Tablets:

Compressed tablets were examined under the magnifying lens for the shape of the tablet.

Tablet Dimensions:

Thickness and diameter were measured using a calibrated varniear caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

Determination of hardness of tablet:

Randomly sampled twenty tablets in each batch of formulations should be used for the determination of hardness with the help of Monsanto type hardness tester.

Determination of weight variation:

Twenty tablets selected at the random are weighed accurately and the average weight of the tablet is calculated. Then the deviation of individual weight from the average weight is calculated.

Determination of thickness of the tablet[51]:

The individual crown – to – crown thickness of ten tablets is determined using slide calipers for each batch.

Measurement of Floating Capacity[52]:

Three individual tablets are put in individual flask containing 400ml of 0.1(N) HCL solutions. Then the time in minutes for each tablets to go from the bottom to the top of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) are measured. The sample mean and standard deviation are then calculated.

Measurement of the Density of the formulation[53]:

The apparent densities of the tablets are calculated from their volumes and masses in triplicate. The volume V of the cylindrical tablets are calculated from their height h and radius (both determined with a micrometer gauge) using the mathematical equation for a cylinder

$$(V = A \times r2 \times h).$$

Determination of drug content in tablets:

Three tablets from each batch are selected randomly and transferred to a 100ml volumetric flask filled up with 0.1(N) HCL. Kept it for 48hours then took 1ml from each of volumetric flask and transferred to the test tubes. Samples are then filtered, suitably diluted and analyzed spectrophotometrically at a suitable wavelength.

In-vitro dissolution study:

The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 1h, 2h, 3h, 4h, 5h, 6h, 8h, 10 h and 12h. The volume of dissolution fluid adjusted to 900 ml by replacing fresh 5ml of dissolution medium after each sampling. The release studies were conducted with 3 tablets, and the mean values were plotted versus time. Each sample was analyzed at maximum wavelength using double beam UV visible spectrophotometer against reagent blank and the corresponding concentration was determined from the respective calibration curve.

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)[54].

Swelling Study:

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.

$$\mathbf{WU = (W1 – W0)/ W0 \times 100}$$

Where, **Wt** = Weight of dosage form at time t.

W0 = Initial weight of dosage form.

DRUGS USED IN FLOATING DRUG DELIVERY SYSTEM[55]

Table 1: List of Drugs along with Floatable Drug Delivery Systems:

Dosage form	Drug
Microspheres	Aspirin, Grisiofulvin, pnitroanilline, Ibuprofen, Terfinadine, Tranilast
Granules	Diclofenac sodium, Indomethacin, Prednisolone
Films	Cinnarizine
Powders	Several basic drugs
Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, Misoprostol, 1-Dopa,benserazide, Propranolol HCl, Ursodeoxycholic acid.
Tablets/pills	Acetaminophen, Acetyl salicylicacid, Amoxicillin trihydrate, Ampicillin, Atenolol, Chloropheniramine, Cinnarizine, Diltiazem, Fluorouracil, Isosorbide mononitrate, Verapamil HCl Isosorbide dinitrate, p-amino benzoicacid, rednisolone, Quinidine gluconate, Theophylline,

Table 2: Marketed Products of Floating Drug Delivery System[56]

Drug	Brand name
Diazepam Floating capsule	Valrelease®
Benserazide and L-Dopa	Madopar®
Aluminium–Magnesium antacid preparation	Topalkan® AlmagateFlot-Coat®
Ciprofloxacin	Cifran OD
Metformin HCl	Glumetza GRTM
Misoprostal	Cyotec Liquid
Aluminium Hydroxide	Gavison
Ferrous sulphate	conviron

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows [57].

Sustained Drug Delivery:

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral controlled release formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Eg. 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 hrs) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hrs).

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. 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.

Absorption Enhancement:

Drugs that have poor bioavailability because of sites specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. Eg. A significantly increase in the bioavailability of floating dosage forms(42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).

CONCLUSION:

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. One of the most feasible approaches for achieving a prolonged and predictable dug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using Gastroretentive dosage forms that will provide us with new and important therapeutic options. Floating matrix tablets are designed to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability The FDDS has an additional advantage for drugs that are absorbed primarily in the upper part of the GIT, *i.e.*, the stomach, duodenum, and jejunum. 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 and also beneficial strategy for the treatment of gastric and duodenal cancers. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying. The floating concept can also be utilized in the development of various anti-reflux formulations. The most important criteria for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid.

And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half life.

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