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*Review Article*

# FLOATING DRUG DELIVERY SYSTEMS: GASTRORETENTIVE APPROACH TO ORAL CONTROLLED DRUG DELIVERY

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## ABSTRACT

Oral controlled release delivery systems are programmed to deliver the drug in predictable time frame that will increase the efficacy and minimize the adverse effects and increase the bioavailability of drugs. Recent technological and scientific research has been devoted to the development of rate controlled drug delivery systems to overcome physiological adversities such as short gastric residence times and unpredictable gastric emptying times. Differences in gastric physiology such as gastric pH and motility exhibit both intra and inter subject variability demonstrating significant impact on gastric residence time and drug delivery behavior. This triggered an increased interest towards formulation of novel delivery systems which retained in the stomach for prolonged and predictable period of time. Several approaches such as floating drug delivery systems (FDDS) also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, bioadhesive systems, modified shape systems, high density systems or other delayed gastric emptying devices. This review article is in pursuit of giving detailed information on the pharmaceutical basis of their design, classification, advantages, *in vitro* and *in vivo* evaluation parameters, and the future potential of FDDS.

**Key Words:** Floating drug delivery system, Gastric residence time, Swelling index, Buoyancy.

## INTRODUCTION

Gastroretentive systems remain in the gastric region for several hours and prolong the gastric residence time of drugs hence it improves bioavailability, reduces wastage of drug, and improves solubility for drugs that are less soluble in a high pH environment.

Gastroretention helps to provide better availability of new products with substantial benefits for patients and new therapeutic possibilities [1, 9, 12, 29].

In the past few decades gastric retention has received significant interest as the conventional oral delivery systems have shown some limitations related to fast gastric emptying time. A gastro retentive dosage form (GRDF) can overcome this problem and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments [23].

The factors which affect the absorption of oral dosage form are First Pass Metabolism, Absorption Windows, Bioavailability Problem, Extended Dosage Regimen, Gastric Emptying Time, effect of $P^H$ on Drugs and Enzymatic Degradation in
Gastro intestinal Tract.

Sustained Release & Controlled Release Drug Delivery System is the Pharmaceutical approach mainly used for overcoming the problem related with oral drug delivery system [2].In sustained release system, the drug is slowly released at an unpredictable rate, from the dosage form

Controlled drug delivery is one which delivers the drug for a specified period of time, at a predetermined rate, for locally or systemically [2, 5].

Controlled-release drug delivery systems (CRDDS) having advantages like maintenance of optimum therapeutic drug concentration in blood for extended time period with predictable and reproducible release rates; reducing frequency of dosing and wastage of drugs; enhancement of activity of duration for short half-life drugs; optimized therapy; elimination of side effects and better patient compliances [3, 4, 16].

An oral controlled drug delivery systems development requires an understanding of the three aspects of the system, namely.

1. The physiochemical characteristics of the drug
2. Anatomy and physiology of GIT
3. Characteristics of Dosage Forms [6]

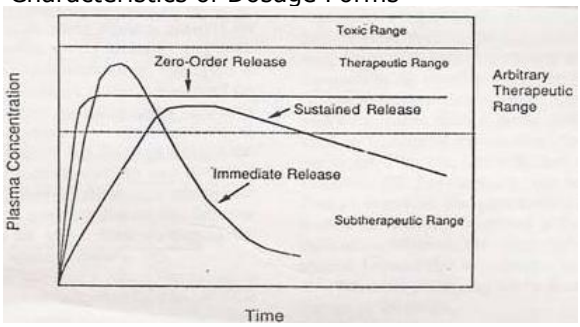


**Fig.1. Drug level verses time profile showing differences between zero order, controlled releases, slow first order sustained release and release from conventional tablet.**

Controlled drug delivery systems are of many types.

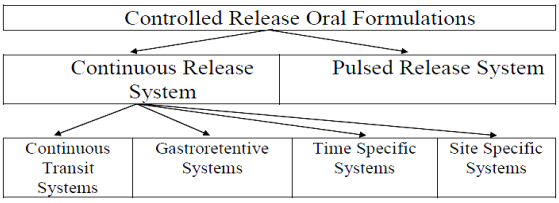


**Fig.2.Types of controlled release formulation** [7]

Now a days gastroretention is a major approach to overcoming the problems associated with other oral drug delivery system.

**Suitable Drugs for Gastroretention**

The dosage form must satisfy certain requirements to achieve gastric retention in the stomach. The dosage form. It must be able to withstand the forces of peristaltic waves in the stomach with the constant contractions and grinding and churning mechanisms. As a gastric retention device, it must resist premature gastric emptying. Once its purpose has been served, the device should be removed from the stomach with ease [8]. Sustained release prolongs the contact time of the agent from where absorption occurs and contact time is limited in the stomach or in the upper part of the small intestine.

Drugs that the stomach does not readily absorb are preferred as sustained release formulations and Drugs that are characterized by better absorption properties at the upper parts of the GIT but have poor colonic absorption are suitable candidates for controlled release gastroretentive dosage forms.

1. Narrow absorption window in GI tract, e.g., riboflavin and Levodopa [19].
2. Basically absorbed from stomach and upper part of GIT, e.g., chlordiazepoxide and cinnarazine.
3. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.
4. Locally active in the stomach, e.g., antacids and Misoprostol.
5. Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole [9].

In floating drug delivery system (FDDS), for maximal gastrointestinal absorption of drugs and site-specific delivery one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT [10].

**Basic Gastrointestinal Tract Physiology** [12, 18]

Stomach is a short-term storage reservoir, consumed large meal quickly. Its main function is to process and transport food. Protein's enzymatic digestion is started in stomach. Liquefied food stuffs after mixing and grinding with gastric secretions by vigorous contractions of gastric smooth muscle is slowly released into the small intestine for further processing [30].

Anatomically fundus, body, and antrum (pylorus) are 3 regions of the stomach. Proximal part is 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 [31].

It has been reported that the mean value of pH is 1.1± 0.15 in fasted healthy subjects. But, the pH may rise to levels in the 3.0 to 4.0 level due to the buffering capacity of proteins when food comes into the stomach. However, in fasted state, basal gastric secretion in women is slightly lower than that of men [34].

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 interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) occurs. It is an interdigestive series of electrical events, which cycle both through stomach and intestine every 2 to 3 hours [32] and is further divided into following 4 phases [33, 20]

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 10 to 20 minutes. It is also known as the housekeeper wave. 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.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

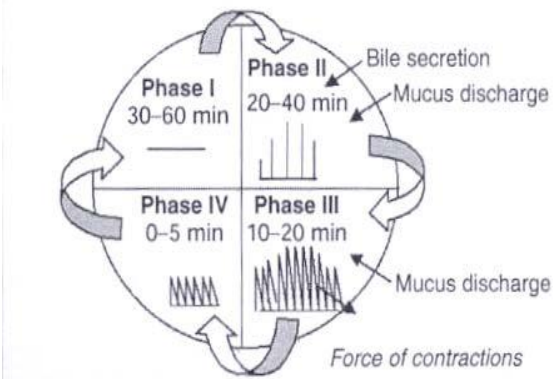


**Fig.3. Motility pattern in GIT**

In digestive motility pattern from fasted to that of fed state the pattern of contractions changes after the ingestion of a mixed meal which results in reducing the size of food particles (to less than 1 mm) and comprises continuous contractions as in phase II of fasted state. These contractions propelled food particles toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slow down of gastric emptying rate [25]. From the result of Scintigraphic studies determining gastric emptying rates orally administered controlled release dosage forms are subjected to basically 2 complications such as short gastric residence time and unpredictable gastric emptying rate[10].

**Factors Affecting Gastric Residence Time of FDDS**

**a) Formulation factor**

**Size of tablets:** Large tablets are expelled during the house keeping waves and Small ones are emptied from the stomach during the digestive phase [35]. But in case of the nonfloating dosage units sank and remained in the lower part of the stomach whereas floating dosage units remained buoyant regardless of their sizes on the gastric contents throughout their residence in the

gastrointestinal tract. During digestive phase floating units were protected from the peristaltic waves away from the gastro-duodenal junction and the nonfloating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase [36].

**Density of tablets:** A density of less than that of gastric contents i.e. less than 1.0 g/ml has been reported. However, the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities as shown by floating force kinetics of such dosage form [37].

**Shape of tablets:** For gastric retention potential six shapes (ring, tetrahedron, cloverleaf, string, pellet, and disk) were screened *in vivo*. The tetrahedron (each leg 2cm long), rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr [38].

**Viscosity grade of polymer:** Viscosity of polymers and their interaction are greatly affected by drug release and floating properties of FDDS. 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. As polymer viscosity is increase there is decrease in the release rate was observed with it [39].

**b) Idiosyncratic factors**

**Gender:** Men have faster gastric emptying time than women. 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 [30].

**Age:** Low gastric emptying time is observed in elderly than do in younger subjects. In gastric and intestinal transit time Intrasubject and intersubject variations are observed. Elderly people, especially those over 70 years have a significantly longer GRT [40].

**Posture**

**i) Upright position:** An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size [40].

As 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 while floating dosage forms show prolonged and more reproducible GRTs [41].

**ii) Supine position:** In supine subjects large dosage forms experiences prolonged retention (both conventional and floating). 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 [42].

**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. Increase gastric emptying time occur with the coadministration of GI-motility decreasing drugs [42].

**Feeding regimen**

In the presence of food gastric residence time increases and at the most favorable site of absorption increased drug dissolution of the dosage form. After a meal of fats and proteins a GRT of 4-10 h have been reported [43].

**APPROACHES TO GASTRORETENTION**

Several techniques are reported in the literature to increase the gastric retention of drugs [42-44, 14].

1) **High density systems:** This system used diluents such as barium sulphate (density= 4.9), zinc oxide, titanium oxide, and iron powder. These systems retained in the rugae of stomach and it withstands its peristaltic movements, having a density of ~3g/cm$^3$ [14, 42, 45].

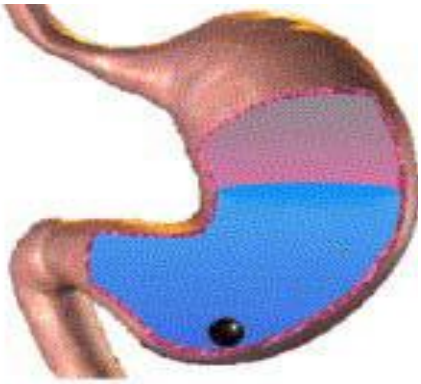

**Fig.5. High density systems** [9]

There is a difficulty in manufacture of such a system with a large amount of drug (>50%) and to achieve the required density of 2.4-2.8g/cm$^3$. High density system is shown in Fig.5.

**2) Swelling and expanding systems:** Although these are Superporous hydrogels [24], also called as "Plug type system", having tendency to remain logged in the pyloric sphincters. These form polymeric matrices and reside in the gastric cavity for several hours in fed state [46].Swelling system is shown in Fig.6.

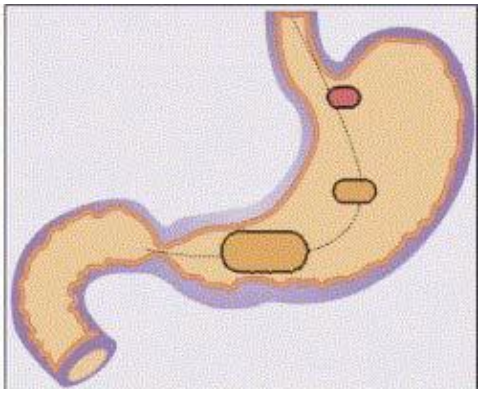

**Fig.6. Swellable tablet in stomach**

A polymer having appropriate molecular weight and swelling properties is selected. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical cross links in the hydrophilic polymer network. Cross linking prevents the dissolution of polymer as well as retards the swelling ability of the system and maintains its

physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer [47].

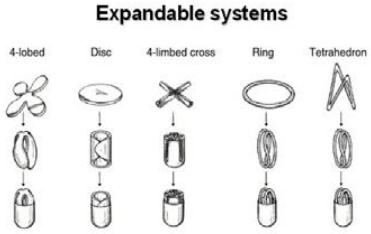


**Fig.7. Different geometric forms of unfoldable systems** [24]

**3) Incorporating delaying excipients:** By decreasing the gastric emptying rate and permitting considerable prolongation of the drug release by feeding of digestible polymers or fatty acid salts that changes the motility pattern, of the stomach to a fed stage is another approach of gastro retentive drug delivery. Incorporating delaying excipients like trietanolamine myristate in a delivery system gives prolongation of GRT [48].

**4) Modified systems:** Systems with non disintegrating geometric shape which extend the GRT depending on size, shape and flexural modules of drug delivery device molded from silastic elastomers or extruded from polyethylene blends [49]. Different geometric forms of unfoldable systems are given in Fig.7.

**5) Mucoadhesive & bioadhesive systems:** Bioadhesive polymers which can adhere to the epithelial surface in the stomach are used in bioadhesive drug delivery system. This system used to localize a delivery device within the lumen to enhance the drug absorption in a site specific manner. Polycarbophil, carbopol, lectins, chitosan, CMC and gliadin etc are most promising excipients used commonly in these systems [50, 51].

**6) Floating systems**

Floating drug delivery systems (FDDS) is also known as hydrodynamically balanced system (HBS) having bulk density less than gastric fluids and without affecting the gastric emptying rate remain buoyant in the stomach for a prolonged period of time. The drug is released slowly at the desired rate from the system when the system is floating on the gastric contents. After release of drug, the residual system is emptied from the stomach [27]. Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air or inert gas.

**Mechanism of Floating Drug Delivery Systems** [17]

Floating drug delivery systems (FDDS) is floating on the gastric contents (given in the Fig. 8a), the drug is released slowly at the desired rate from the system. The residual system is emptied from the stomach after release of drug. This results in a better control of the fluctuations in plasma drug concentration and an increased GRT. To allow the proper achievement of the buoyancy retention principle needs minimal gastric content. 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 (Fig.8b). 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 [58].

F = F buoyancy - F gravity = (Df - Ds) gv

Where, F= total vertical force

Df = fluid density

Ds = object density

v = volume and

g = acceleration due to gravity

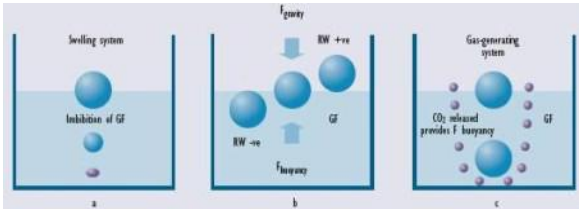


**Fig.8.The mechanism of floating systems**

**Classification of FDDS Based On Mechanism of Buoyancy**

**A) Single unit:** Single unit dosage form is easy to develop but there is a risk of losing their effects too earlier due to their all-or-none emptying from the stomach and this leads to high variability in bioavailability and local irritation as large amount of drug delivered at a particular site of the gastro intestinal tract [52].

**Noneffervescent systems**

One or more gel forming, highly swellable, cellulosic hydrocolloids (e.g. hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxyl propyl methyl cellulose [HPMC] and sodium carboxy methyl cellulose), polysaccharides, or matrix forming polymers (e.g.polycarbophil, polyacrylates, and polystyrene) are incorporated in high level (20-75% w/w) [53,54] in the manufacturing of tablet or capsule and mixed thoroughly. This dosage form swells in contact with gastric fluids and attains a bulk density of < 1 after oral administration. Due to air entrapped within the swollen matrix dosage form becomes buoyant. Formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass. Sheth and Tossounian [59] developed a HBS capsule containing a mixture of a drug and hydrocolloids. The capsule shell dissolves upon contact with gastric fluid; the mixture swells and forms a gelatinous barrier which gives buoyancy for an extended period of time in the gastric juice.

**Effervescent systems or gas generating systems** [9]

With the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds e.g. sodium bicarbonate, tartaric acid, and citric acid these matrix types of systems are formulated. When these formulations come in contact with the acidic gastric contents, $CO_2$ is liberated and gets entrapped in swollen hydrocolloids, which gives buoyancy to the dosage forms. The optimal stoichiometric ratio of citric acid

and sodium bicarbonate is 0.76:1 for gas generation.

**B) Multiple units**

The major problems like sticking together or being obstructed in gastrointestinal tract are associated with Single unit formulations which may produce irritation. Multiple unit systems avoid the 'all-or-none' gastric emptying nature of single unit systems along with lowers the probability for dose dumping and reduces the intersubject variability in absorption [55].

**Noneffervescent systems**

On noneffervescent multiple unit systems little or no much report was found in the literature as compared to the effervescent systems. In the development of such system contain indomethacin and chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported in which mixture of drug, chitosan and acetic acid is extruded through a needle then the extrudate is cut and dried. In the acidic media chitosan hydrates were float and by modifying the drug-polymer ratio the required drug release could be obtained [9].

**Effervescent systems**

A multiple unit system consists of calcium alginate core and calcium alginate/PVA membrane. Both separated by an air compartment was prepared. The PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment in presence of water. Due to increase in molecular weight and concentration of PVA, enhancement of floating properties of the system occurs. For the preparation of floating calcium alginate beads freeze-drying technique is used in which sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, due to the formation of calcium alginate[9]. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behavior of radio labeled floating beads and compared with non-floating beads in human volunteers using gamma scintigraphy. For floating beads prolonged gastric residence time of more than 5.5 h was observed. The nonfloating beads had a shorter residence time with a mean onset emptying time of 1 hr [56].

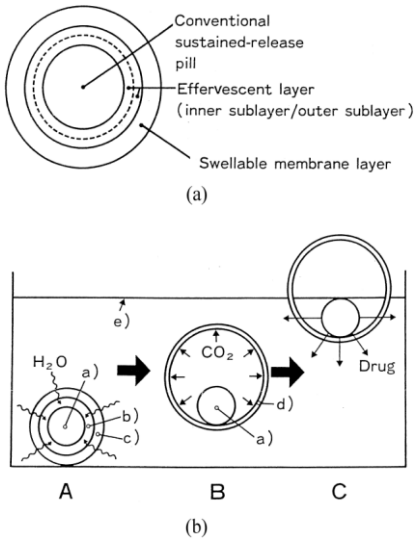


**Fig. 9 (a) A multiple-unit oral floating dosage system (b) Stages of floating mechanism: (A) penetration of water; (B) generation of $CO_2$ and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37$^0$C)** [14].

**Floating microspheres**

Floating microspheres increases its residence time in the stomach without contact with the mucosa as it is a controlled release system. Simple solvent evaporation, solvent diffusion and evaporation are the techniques involved in their preparation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers, Such as polycarbonate, Eudragit® S and cellulose acetate are used in the preparation of hollow microspheres. By optimizing the amount of polymer and the polymer plasticizer ratio the drug release can be modified [57].

**C) Raft forming systems**

The basic mechanism involved in the raft formation includes in contact with gastric fluids the formation of viscous cohesive gel, in that each portion of the liquid swells forming a continuous layer called a raft. By the formation of $CO_2$ the raft floats which create buoyancy and act as a barrier to prevent the reflux of gastric contents like HCl and enzymes into the esophagus. $CO_2$ gas generation takes place due to presence of a gel forming agent and alkaline bicarbonates or carbonates, make the system less dense and float on the gastric fluids [60]. Reckitt and Colman Products Ltd. have

formulated such system in the treatment of H.pylori infections of GIT.

**Advantages of Floating Drug Delivery Systems** [9, 61]

1. For drugs absorbed through the stomach, e.g. ferrous salts, antacids.
2. HBS formulation may be useful for the administration of aspirin and other similar drugs which cause irritation on the stomach wall when come in contact with it.
3. Prolongs release floating dosage forms, tablet or capsules dissolve in the gastric fluid after emptying of the stomach contents would be available for absorption in the small intestine. 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.
4. For drugs meant for local action in the stomach e.g. antacids.
5. In certain type of diarrhea, poor absorption is expected as there is a vigorous intestinal movement and a short transit time may occur. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
6. FDDS improves patient compliance by decreasing dosing frequency.
7. 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.
8. Better therapeutic effect of short half-life drugs can be achieved.
9. Gastric retention time is increased because of buoyancy.
10. Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.
11. 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.
12. The efficacy of the medicaments administered utilizing the sustained release principle of floating formulation has been found to be independent of the site of particular medicaments.
13. Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric-coated LASIX-long product (29.5%).
14. They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid because their bulk density is lower than that of the gastric fluids [11, 21].

**Limitations of Floating Drug Delivery Systems** [2, 9, 11, 17]

1. A high level of fluid in the stomach is required for drug delivery to float and work efficiently.
2. Drugs which have stability and solubility problems in GIT are not suitable candidates.
3. Drugs such as Nifedipine, which under goes first pass metabolism may not be desirable for the preparation of these types of systems.
4. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
5. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
6. Drugs that cause irritation and lesion to gastric mucosa are not desirable.
7. High variability in gastric emptying time due to its all or non-emptying process.
8. 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.
9. The floating systems in patients with achlorhydria can be questionable in case of swellable system.
10. Retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.
11. The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

**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 [70-73].

**Pharmacokinetic aspects:**

**Absorption window**: Various experimental techniques are available that allow 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, following sustained presentation of the drug to the transporting enzymes the efficacy of the transport activity may increase in comparison to non-control release mode of administration.

**Enhanced bioavailability:** The drugs showing 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, in comparison to administration of simple CR polymeric formulations, the bioavailability of control release (CR) floating systems of Riboflavin and Levodopa are significantly enhanced. 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 [74].

**Enhanced first pass biotransformation**: It is a similar in fashion to increased efficacy of active transporters exhibiting capacity limited activity, when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input the pre-systemic metabolism of the tested compound may be considerably increased.

**Improved bioavailability due to reduced P-glycoprotein (P-gp) activity in the duodenum:** In contrast to the higher density of CYP3A4 at the upper part of the intestine, along the intestine P-gp mRNA levels increase longitudinally 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, as compare to immediate and CR dosage forms floating systems may elevate absorption.

**Reduced frequency of dosing:** For drugs having 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 is associated with improved patient compliance, and thereby improves therapy.

**Targeted therapy for local ailments in the upper GIT:** For local therapy in the stomach and the small intestine the prolonged and sustained administration of the drug from the floating systems to the stomach may be advantageous to increase gastric retention as well as bioavailability.

**Pharmacodynamic Aspects of FDDS:**

**Minimized Adverse Activity at the Colon:** HBS systems retain the drug at the stomach minimizes the amount of drug that reaches the colon. So, adverse activities of the drug in colon may be prevented. This Pharmacodynamic aspect provides the rationale for floating drug delivery 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 [28].

**Reduced Fluctuations of Drug Concentration:** As compared to the immediate release dosage forms giving continuous input of the drug following floating system administration produce blood drug concentrations within a narrower range. 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 [28].

**Improved Receptor Activation Selectivity:** It is possible to obtain certain selectivity in the elicited pharmacological effect of drugs by minimizing of fluctuations in drug concentration that activate different types of receptors at different concentrations.

**Reduced Counter Activity of Body:** Slow release of drug gives higher drug efficiency in body minimizes the counter activity [11].

***IN VITRO* AND *IN VIVO* EVALUATION PARAMETERS OF STOMACH SPECIFIC FDDS**

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro and floating behavior show prolonged gastric residence in vivo. Although, in vitro floating behavior alone is not sufficient proof for efficient gastric retention so *in vivo* studies can provide definite proof that prolonged gastric residence is obtained [9].Various parameters that need to be evaluated in gastroretentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multi-particulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed [10].

**I. Pre-compression parameters**: angle of Repose (θ) [62], 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 Vernier 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:** To find out weight variation, 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight [75].

| S.No. | Average Weight of Tablet | % Deviation |
|---|---|---|
| 1 | 80 mg or less | 10 |
| 2 | More than 80 mg but less than 250 mg | 7.5 |
| 3 | 250 or more | 5 |

**Fig.10. Specifications for Tablets as Per Pharmacopoeia**

**Determination of thickness of the tablet [63]:** The individual crown – to – crown thickness of ten tablets is determined using slide calipers for each batch.

**Measurement of the Density of the formulation [67]:** 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 ($V = A \times r^2 \times h$).

**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 USP type II (paddle) apparatus at 100 rpm. 10ml 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 10ml 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 *in-vitro* buoyancy was determined by floating lag time and floating time. The tablets were placed in dissolution vessel containing 900 ml of 0.1N HCl. 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) [68].

**Swelling Study:** Weight gain or water uptake can be studied by considering the swelling behavior of Floating dosage form. The study is done by immersing the dosage form in a beaker containing simulated gastric fluid containing 900 ml of 0.1N HCl at 37°C and determining the dimensional changes like tablet diameter and/ or thickness at regular 1-h time intervals until 24 h, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then reweighed and WU is measured in the terms of percent weight gain, as given by equation

**WU = (Wt – Wo) X 100 / Wo**

In which Wt and Wo are the weights of the dosage form at time t and initially, respectively [9].

**X-ray/Gamma scintigraphy**

For *in vivo* studies, X-Ray/Gamma Scintigraphy is the main evaluation parameter for floating dosage form. It is a technique where by the transit of a dosage form through its intended site of delivery can be non-invasively imaged *in vivo* via the judicious introduction of an appropriate short lived gamma emitting radioisotope. In each experiment, the animals are allowed to fast overnight with free access to water and a radiograph is made just before the administration of the floating tablet to ensure the absence of radio-opaque material. Visualization of dosage form by X-ray is due to the inclusion of a radio-opaque material. The formulation is administered by natural swallowing followed by 50 mL of water. The radiographic imaging is taken from each animal in a standing position, and the distance between the source of X-rays and the animal should kept constant for all imaging, so that the tablet movement could be easily noticed. Gastric radiography was done at 30-min time intervals for a period of 5 h using an X-ray machine. The inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner. But the main drawback of γ- scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceutical [9,65].

**Pharmacokinetic studies**

Pharmacokinetic studies include AUC (Area under Curve), C max, and time to reach maximum plasma concentration (Tmax) were estimated using a computer. Statistical analyses were performed using a Student t test with p, 0.05 as the minimal level of Significance [66].

**Specific Gravity:** Displacement method is used to determine the specific gravity of floating system using benzene as a displacing medium [9].

**Gastroscopy:** Gastroscopy is used to inspect visually the effect of prolonged stay in stomach milieu on the FDDS. It used with a fibereoptic and video systems. It comprises of peroral endoscopy, alternatively FDDS may be drawn out of the stomach for more detailed evaluation[15].

**Ultrasonography:** Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs. Therefore, the characterization included assessment of intragastric location of the hydrogels, solvent penetration into the gel and interactions between gastric wall and FDDS during peristalsis[15].

**$^{13}$C Octanoic Acid Breath Test:** $^{13}$C Octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates $CO_2$ gas which comes out in breath. The important Carbon atom which will come in $CO_2$ is replaced with $^{13}$C isotope. So time up to which $^{13}CO_2$ gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no $CO_2$ release. So this method is cheaper than other [22].

**Magnetic Marker Monitoring [11]:** In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. It is radiation less and so not hazardous method.

**APPLICATIONS**

**Sustained Drug Delivery**

To overcome problems such as gastric residence time in the GIT encountered with oral control release formulations which have a bulk density

<1 hydro dynamically balanced system can used, as a result of which they can float on the gastric contents and remain in the stomach for long periods (HBS). These systems are relatively larger in size, so their passage from the pyloric opening is prohibited [10, 28]. Recently sustained release floating capsules of Nicardipine hydrochloride were developed and were evaluated in vivo [26, 27, 10].

The drugs with short half life, a sustained and slow input from FDDS may result in flip-flop pharmacokinetics and it reduces the dose frequency. This feature is associated with improved patient compliance and thus improved therapy [11].

**Bioavailability Enhancement** [15]

Drugs that have site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems due to their poor bioavailability, thereby maximizing their absorption [10, 28]. The absorption of bromocriptine in conventional dosage form is limited to 30% from the gastrointestinal tract but in case of hydrodynamically balanced system (HBS) of the bromocriptine can enhance the absorption [10, 27].

**Site-Specific Drug Delivery**

This system have more advantages for the drugs like riboflavin and furosemide [13] which are specifically absorbed from stomach or the proximal part of the small intestine,. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels also reduce the dosing frequency with prolonged gastric availability and limits the systemic exposure to the drug which resulted to reduce side effects that are caused by the drug in the blood circulation [10, 28].

**Table.1. Marketed Products of Floating Drug Delivery System** [69]

| DRUG | BRAND NAME |
|---|---|
| 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 |

## DISCUSSION

Oral drug administration is more popular than other type of pharmaceutical dosages form.

Drugs that are easily absorbed from the stomach and have a short half-life are eliminated quickly from the blood circulation, require frequent dosing. To avoid this problem, the oral Gastroretentive formulations have been developed in an attempt to release the drug slowly into the Gastric region.

Floating drug delivery system is one of these oral dosage system forms and become an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. This drug delivery system not only prolongs GI residence time but does so in an area of the GI tract that could maximize drug reaching its absorption site in solution and hence ready for absorption.

In addition, the identification of new diseases and the resistance shown towards the existing drugs considered the need for the introducing new therapeutic molecules.

The study of the effect of various geometric shapes in a more excessive manner than previous studies on gastroretentivity needs to be developed. 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 investigations can be concentrated on the concept of design of novel polymers according to clinical and pharmaceutical need. Moreover, further studies are expected in the future that would ultimately lead to improved efficiencies of various types of pharmacotherapies.

## CONFLICT OF INTEREST

Authors declare no conflict of interest.

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