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FLOATING DRUG DELIVERY SYSTEM: AN APPROACH TO ORAL CONTROLLED DRUG DELIVERY

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ABSTRACT

Recent technological and scientific research has been devoted to the development of controlled drug delivery systems to overcome unpredictable gastric emptying times and short gastric residence times. Gastric emptying, a complex process, makes in-vivo performance of the drug delivery systems uncertain. In order to avoid this variability, efforts had been made to increase the retention time for more than 12 hours. Incorporation of the drug in a CR-GRDF which can remain in the gastric region for several hours, would significantly extend the gastric residence time and improve bioavailability, reduce drug wastage and enhance the solubility that are less soluble in high pH environment. The recent developments of FDDS including the physiological and formulation variables approaches to design single-unit and multiple-unit floating systems & their classification & formulation aspects were covered in detail. This review article is in pursuit of enlisting detailed information on the pharmaceutical basis of their design, classification, advantages *and in-vitro* evaluation parameters.

Key Words: Gastric emptying, floating drug delivery systems, single unit, multiple units

INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems. Controlled release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate *[1]*. Although tremendous advances have seen in oral controlled drug delivery system during last two decades. This system has been of limited success. This approach is be filled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the

gastrointestinal tract (GIT) due to variable gastric emptying and motility. *[2]*

Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of the drugs are absorbed in the stomach or the upper part of the small intestine *[3]*.

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control-emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period than conventional dosage forms. Several difficulties faced in designing of controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa *[4]*. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed.

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients *[5]*.

Several approaches have been attempted in the preparation of gastro-retentive drug delivery systems. These include floating systems, swellable and expandable systems, high-density systems, bioadhesive systems, altered shape systems, gel-forming solution or suspension systems and sachet systems *[6]*.

FLOATING DRUG DELIVERY SYSTEM:

Davis first described floating drug delivery systems in 1968. These systems were used to prolong the gastric residence time of drug delivery systems. They remain buoyant in the stomach for prolonged period without affecting the gastric emptying rate of other contents. A floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract (GIT), are unstable in lower parts of GIT, or are poorly absorbed in the intestine. This type of formulation also used for drugs absorbed only in the initial part of the small intestine, in the same way as ranitidine. These systems help in continuously releasing the drug before it reaches the

absorption window, thus ensuring optimal bioavailability *[7]*.

Floating drug delivery systems (FDDS) have bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system, after release of drug; the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration *[8]*. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal *[9]*.

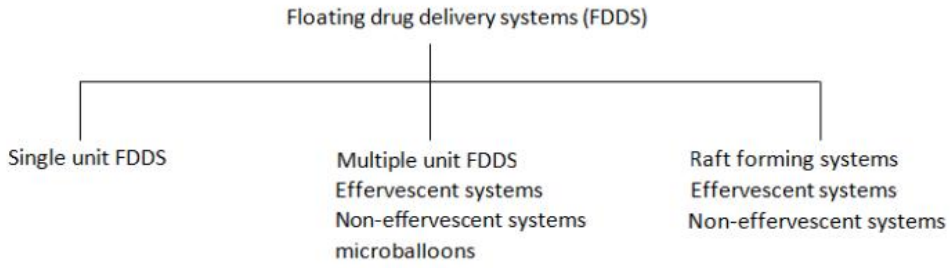

Table 1: Patent on FDDS

S. No.	Type of formulation	Patent no	Reference
1	Gastro retentive dosage form	U.S-7, 413,752	10
2	Multiple unit floating dosage form	European patent (EP) 10697	11
3	Bilayer tablet	EP-002445	12
4	Floating Tablet	U.S-66, 352279	13
5	Microspheres	U.S-6207197	14
6	3-layer tablet	U.S-5780057	15
7	Foams (or) hollow bodies	U.S-5626876	16
8	Floating tablet	U.S-5169639	17
9	Granule	U.S-4844905	18
10	Floating capsules	U.S-4814178, 79	19
11	Floating device	U.S-4055178	20
12	Floating capsule	U.S-4126672	21
13	Empty globular shells	U.S-3976164	22

Selection criteria of drugs for gastroretention

Delivery of the Drugs in continuous and controlled manner have a lower level of side effects and provide their effects without the need for repeated dosing or with a low dosage frequency. Sustained release in the

stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, from where absorption occurs and contact time is limited. Appropriate candidate for controlled release gastro-retentive dosage forms are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

1. Narrow absorption window in GI tract, e.g., riboflavin and levodopa *[1]*.
2. Primarily absorbed from stomach and upper part of GIT, e.g., calcium supplements, chlordiazepoxide and cinnarazine *[8]*
3. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
4. Drugs that act locally in the stomach, e.g., antacids and misoprostol *[8]*.
5. Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori *[1]*

Table 2: List of Drugs can be formulated as Floating Drug Delivery Systems

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

APPROACHES TO DESIGN FLOATING DOSAGE FORMS:

The following approach has been used for the design of floating dosage forms of single and multiple unit systems.

***Single-Unit Dosage Forms*:**

In Low-density approach, the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also obtained by using a fluid-filled

system that floats in the stomach. In coated shells popcorn, pop rice, and polystyrol has been exploited as drug carriers. A sugar polymeric material such as methacrylic polymer and cellulose acetate phthalate has been used to undercoat these shells. These were further coated with a drug-polymer mixture. The polymer of choice can be either ethyl cellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. *[5]*

Fluid-filled floating chamber type of dosage forms includes incorporation of a gas-filled floatation chamber into a micro porous component that houses a drug reservoir. 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 were sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behavior. The device is of swallow able size, remains afloat 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) were 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 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. *[9]*

Single unit dosage forms are easiest to develop but suffers from the risk of losing their effects too early due to their all or none emptying from the stomach and, thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract. *[1]*

***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 is devoid of any of the above-mentioned disadvantages of single-unit formulations. In pursuit of this endeavor, many multiple-unit floatable dosage forms have been designed.

Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microsponges also referred to as “microballoons,” have been prepared. Microspheres have a characteristic

internal hollow structure and show an excellent in vitro floatability. In Carbon dioxide–generating multiple-unit oral formulations, several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature. These dosage forms excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded *[5]*. Single unit formulations are associated with problems such as sticking together or obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple unit systems avoid the 'all or none' gastric emptying nature of single unit systems. It reduces the inter-subject variability in absorption and the probabilities for dose dumping is lower *[1]*.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS (FDDS):

Floating drug delivery systems are classified depending on the use of 2 formulation variables: effervescent and non-effervescent systems.

***Effervescent Floating Dosage Forms*:**

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid *[23]*. Or matrices containing chambers of liquid that gasify at body temperature *[24,25]*. The matrices fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellifie hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chyme *[23]*. The carbon dioxide generating components may be intimately mixed within the tablet matrix, in which case a single-layered tablet is produced *[26]*, or a bilayered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for a SR effect *[27]*. This concept has also been exploited for floating capsule systems *[28]* prepared floating capsules by filling with a mixture of sodium alginate and sodium bicarbonate. The system was shown to float during in vitro tests because of the generation of CO2 that was trapped in the hydrating gel network on exposure to an acidic environment.

***Non-effervescent Floating Dosage Forms*:**

The most commonly used excipients in non-effervescent FDDS are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate,

polyacrylate, polymethacrylate and polystyrene. One of the approaches to the

formulation of such floating dosage forms involves intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier *[29]*. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release since the drug slowly released by a controlled diffusion through the gelatinous barrier. **Sheth and Tossounian** *[30]* postulated that when such dosage forms are exposed to an aqueous medium, the hydrocolloid starts to hydrate by first forming a gel at the surface of the dosage form. The resultant gel structure then controls the rate of diffusion of solvent-in and drug-out of the dosage form. As the exterior surface of the dosage form goes into solution, immediate adjacent hydrocolloid layer become hydrated maintains the gel layer. As a result, the drug dissolves in and diffuses out with the diffusing solvent, creating a 'receding boundary' within the gel structure *[30]*.

ADVANTAGES OF FLOATING ORAL DRUG DELIVERY SYSTEM: ***[1, 31]***

1. 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.
2. The fluctuations in plasma drug concentration are minimized, and concentration dependent adverse effects that are associated with peak concentrations can be prevented.
3. The efficacy of the medicaments administered utilizing the sustained release principle of floating formulation has found to be independent of the site of particular medicaments.
4. Complete absorption of the drug from the floating dosage form is expected even at the alkaline pH of the intestine.
5. Poor absorption is expected when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea. Under such circumstances, it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
6. Maximizing absorption of the drugs with poor bioavailibility because of the site-specific absorption in upper GIT.
7. These can improve the pharmacotherapy of the stomach through local action of the drug used to eradicate H. pylori.

DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM: ***[1, 9]***

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.

2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate e.g. nifedipine.
4. Some drugs present in the floating system causes irritation to gastric mucosa.
5. Drugs, which are irritant to Gastric mucosa, are also not desirable.
6. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the system.

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS:

Various parameters that need to be evaluated in gastroretentive formulation include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, Differential Scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, mechanical properties and X-ray diffraction studies can be performed.

For Single Unit Dosage Forms

(i) **Floating lag time:** It is the time taken by the tablet to emerge onto the surface of dissolution medium and expressed in seconds or minutes. The test for floating time measurement usually performed in stimulated gastric fluid or 0.1 mole.lit-1 HCl maintained at 37°C. It is determined by using USP dissolution apparatus containing 0.1 mole lit^{-1} HCl (900 ml) as the dissolution medium at 37°C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time *[32]*.

(ii) **Invitro drug release and duration of floating:** This is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37 ± 0.2 °c in simulated gastric fluid (pH 1.2 without pepsin). Aliquots of the samples are collected and analyzed for the drug content. The time (hrs) for which the tablets remain buoyant on the surface of the dissolution medium is the duration of floating and is visually observed *[33]*.

For Multiple Unit Dosage Forms

1. Micromeritic Properties

Angle of repose, density, hausner's ratio, and compressibility index is determined by using proper equations

2. Particle Size and Shape

Scanning electron microscopy (SEM) provides higher resolution in contrast to the light microscopy (LM). The most widely used procedures to visualize micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can

be used to determine the shape and outer structure of multiparticulate. LM provides a control over coating parameters in case of double walled micro spheres. The multiparticulate structures can be visualized before and after coating and the change can be measured microscopically. SEM allows investigations of the multiparticular surfaces and after particles cross-sectioned.

3. Entrapment efficiency: The drug extracted by a suitable method, analyzed and is calculated using equation:

$$\% \text{ Entrapment} = \frac{\text{Actual content}}{\text{Theoretical content}} \times 100$$

4. X-Ray/Gamma Scintigraphy:

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form now a day *[34]*. It helps to locate dosage form in the GIT and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner *[35]*. In case of γ-scintigraphy, the γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract *[36]*.

5. In vitro floating ability (Buoyancy %): A known quantity of microspheres are spread over the surface of a USP (Type II) dissolution apparatus filled with 900 ml of 0.1 N HCl containing 0.002% v/v Tween 80 and agitated at 100 rpm for 12 hours. After 12 hours, the floating and settled layers are separated, dried and weighed. The buoyancy can be calculated from the following formula. Buoyancy (%) = Wf / (Wf + Ws) * 100 where Wf and Ws are the weights of floating and settled microspheres respectively.

6. In-Vitro Release Studies:

The release rate of floating microparticulate is determined in dissolution apparatus. A weighed amount of floating microspheres equivalent to dose of drug is taken and placed in the basket of dissolution rate apparatus. The dissolution fluid is maintained at 37 ± 0.5°C at a rotation speed that provides sink conditions during the drug release study.

APPLICATION OF FLOATING DRUG DELIVERY SYSTEMS:

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.

1. *Sustained Drug Delivery*

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period. The problem of short gastric residence time encountered with an oral CR 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 *[9]*.

Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours). Similarly a comparative study between the Madopar HBS and madopar standard formulation was do and it was shown that the drug was released up to 8 hours in vitro in the former case and the release was essentially complete inless than 30 minutes in the latter case.

2. *Site specific drug delivery system*

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 *[9]*. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has 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 approximately1.8 times those of conventional furosemide tablets.

A bilayer-floating capsule was developed for local delivery of misoprostol that is a synthetic analog of prostaglandinE1 used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug wastage could be reduced.

3. *Absorption Enhancement*

Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates 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%).

CONCLUSION:

The currently available polymer-mediated noneffervescent and effervescent FDDS, designed based on delayed gastric emptying and buoyancy principles, appear to be an effective and rational approach to the modulation of controlled oral drug delivery. This is evident from the number of commercial products and a myriad of patents issued in this field. The gastro-retentive dosage forms are used for drugs that have a short half-life and require repetitive dosing at shorter intervals. These are helpful in reducing the dosing interval and reduce the amount of drug to be administered on overall basis. All the approaches of the gastroretentive drug delivery had shown promising role for the sustained effect of the drug on the body. Research has shown that it is not difficult to control the rate of drug release and the extent of drug release. Comparing the non-effervescent systems with the other dosage systems, alginate beads provide good results within vitro as well as in vivo analysis.

A number of researchers have formulated hollow microspheres or microballons and they also show good floating time and release characteristics but their potential has not been fully exploited. Moreover, these multi-particulate systems have lesser chances of dose dumping. The Mucoadhesive systems and the floating systems provide the best results in vitro as well as in vivo and can be easily formulated for the market. Some of the unresolved critical issues related to the rational development of FDDS include:

(1) The quantitative efficiency of floating delivery systems in the fasted and fedstates.
(2) The role of buoyancy in enhancing GRT of FDDS
(3) The correlation between prolonged GRT and SR/PK characteristics.

Finally, with an increasing understanding of polymer behavior and the role of the biological factors mentioned above, it is suggested that future research work in the floating drug delivery systems should be aimed at discovering means to accurately control the drug input rate into the GI tract for the optimization of the pharmacokinetic and toxicological profiles of medicinal agents.

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