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The Need of Floating Drug Delivery System: A Review

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ABSTRACT

The floating drug delivery systems have been extensively used to improve therapy with several drugs. However during development process several difficulties are faced such as inability to restrain and localize the system within desired region of the GIT and its variable as per gastric emptying process. The variability may cause unpredictable bioavailability and time to achieve peak plasma levels. On the other hand, incorporation of the drug in a controlled release gastroretentive dosage forms (CR-GRDF) which can remain in the gastric region for several h would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. This FDDS provides local delivery to specific region like stomach and proximal small intestine and it's also shows better bioavailability and improved therapeutic activity and substantial benefits to patients. The purpose of this paper is to review the recent literature and current technology used in the development of floating drug delivery system.

Key words: Gastroretention, Oral controlled release, floating drug delivery system, hydrodynamically balanced system.

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INTRODUCTION

The main aim of gastric floating drug delivery system to achieve better bioavailability and release of drug from specific system and the high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms. However, this approach is bedilled 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. However, this approach is bedilled 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. Floating DDS provides better bioavailability for the drugs that are unstable in intestinal or colonic environment. To formulate a successful or gastroretentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS)/floating drug delivery system, low density systems, raft systems incorporating alginate gels, bioadhesive or mucoadhesive systems, high density systems, super porous hydrogels and magnetic systems. 0ral route has been the commonly adopted and the most convenient route for the drug administration. It has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other route. Although tremendous advances have been seen in oral controlled drug delivery system in the last two decades, this system has been of limited success in the case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). In the development of oral controlled drug delivery system, one of the main challenges is to modify the GI transit time. Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fasted state of the stomach. Normal gastric residence times usually range between 5 minutes and 2 h. In the fasted state the electrical activity in the stomach – the interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and, hence, the transit of dosage forms. It is characterized by four phases:

- Phase I–Period of no contraction (40-60 minutes),
- Phase II –Period of intermittent contractions (20-40 minutes),
- Phase III–Period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave. (10-20 minutes),
- Phase IV–Period of transition between phase III and phase I (0-5 minutes) [1].

However, this approach is bedilled 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. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose [2]. This has led to the development of oral gastroretentive dosage forms. Gastroretention is essential for drugs that are absorbed from the stomach, drugs that are poorly soluble or degraded by the higher pH of intestine, and drugs with an absorption which can be modified by changes in gastric emptying time. Gastroretentive dosage forms are also useful for local as well as sustained drug delivery for certain conditions, like H. pylori infection which is the cause of peptic ulcers. This dosage form improves bioavailability, therapeutic efficacy and may even also allow a possible reduction in the dose because of steady therapeutic levels of drug, for example furosemide and ofloxacin. The reduction in fluctuations in therapeutic levels minimizes the risk of resistance especially in case of β-lactam antibiotics (penicillins and cephalosporins) [3].

Gastroretensive systems can remain in the gastric region for several h 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 [4].

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Suitable Drug Candidates for Gastroretention

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages 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, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example, material passes through the small intestine in as little as 1-3 h [5].

In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

- Narrow absorption window in GI tract, e.g., riboflavin and levodopa
- Primarily absorbed from stomach and upper part of GIT, e.g., calcium supplements, chlordiazepoxide and cinnarazine.
- Drugs that act locally in the stomach, e.g., antacids and misoprostol.
- Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate

The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in GRDFs that were designed, in large part, based on the following approaches.

- Low density form of the DF that causes buoyancy in gastric fluid [6]
- High density DF that is retained in the bottom of the stomach [7]
- Bioadhesion to stomach mucosa [8].
- Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients [9].
- Expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter [10].

VERIOUS TYPES OF GASTRORETENTIVE DOSAGE FORMS

A. Floating drug delivery systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non-effervescent and gas-generating system.

(a) Non-effervescent systems

This type of system, after swallowing, swells unrestrained via imbibition of gastomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates [11].

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

(i) Colloidal gel barrier system [12]

Sheth and Tossounian first designated this 'hydrodynamically balanced system'. Such a system 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. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysacharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

(ii) Microporous compartment system

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls13. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved 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 stric fluid to an extent that it prevents their exit from the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

(iii) 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 [14]. The beads are then separated, snap-frozen in liquid nitrogen and freeze-dried at 40ºC for 24 h, leading to the formation of a porous system, which can maintain a floating force for over 12 h. These floating beads gave a prolonged residence time of more than 5.5 h.

(iv) Hollow microspheres / Microballoons

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method [15]. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h.

(b) Gas-generating (Effervescent) systems

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid) [15]. The system is so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate [16], multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

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B. Expandable systems

Expandable gastroretentive dosage forms (GRDFs) have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach [17]. Gastroretentivity is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach. Positive results were obtained in preclinical and clinical studies evaluating the GRT of expandable GRDFs. Narrow absorption window drugs compounded in such systems have improved in vivo absorption properties.

C. Bio/Muco-adhesive systems

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach [18]. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc.

D. High-density systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm-3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 h, depending more on density than on the diameter of the pellets19. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm-3.

MECHANISM OF FLOATING SYSTEMS [20]

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (Figure 1a), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Figure 1b). 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

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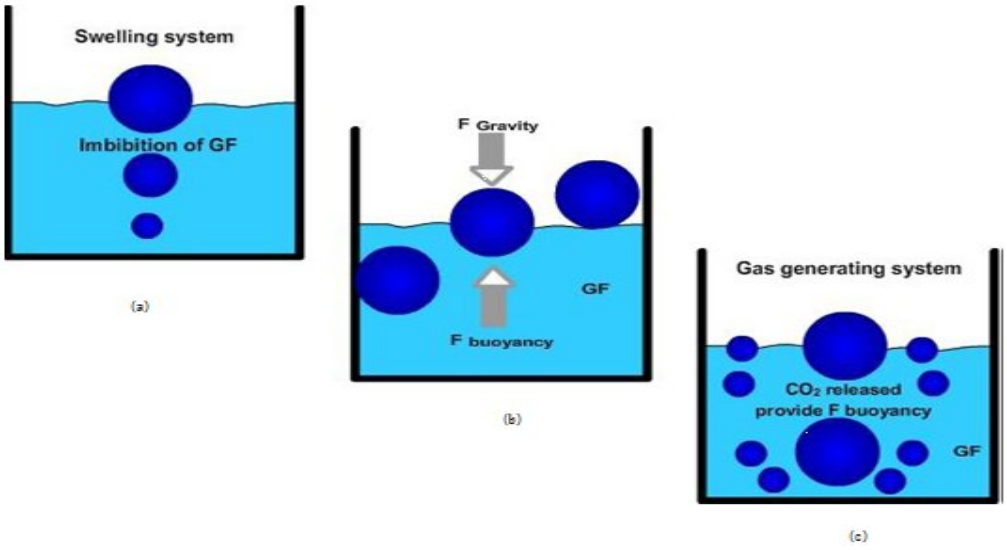
F = F buoyancy - F gravity
= (Df - Ds) gv--- (1)

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

Fig.1.Mechanism of floating systems, GF= Gastric fluid



Advantages of Floating drug delivery system [21, 22]:

1. The gastroretensive systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
2. 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.
3. 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.
4. The gastroretensive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.
5. 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.

Disadvantages of floating drug delivery system:

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.

4. Some drugs present in the floating system causes irritation to gastric mucosa.

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 of time. 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. 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 h) in the sustained release floating capsules as compared with conventional MICARD capsules (8 h) [23].

2. Site-Specific Drug Delivery:

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide.
Eg. 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. [24]

3. Absorption Enhancement:

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.
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%).[24]

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex, sleep and disease state of the individual (e.g., gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents (cisapride and metoclopramide).

1. Density of dosage form

Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention. A density of <1.0 gm/cm3 is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium [25].

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2. Size of dosage form

The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine [26]. Thus the size of the dosage form appears to be an important factor affecting gastric retention.

3. Food intake and nature of food

Food intakes, the nature of the food, caloric content, and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the stomach influences the GRT of the dosage form. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time. In a gamma scintigraphic study of a bilayer floating capsule of misoprostol [27], the mean gastric residence time was 199 ± 69 minutes; after a light breakfast, a remarkable enhancement of average GRT to 618 ± 208 minutes was observed. The above results are supported by the experiments of Whitehead et al[28] which show an increase in the relative heights of the floating units after meal consumption.

4. Effect of gender, posture and age

A study by Mojaverian et al [29] found that females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men. The authors also studied the effect of posture on GRT, and found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. On the other hand, in a comparative study in humans by Gansbeke et al [30], the floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of similar size [31].

Drugs explored in floating dosage forms [32, 33]

Types of dosage forms	Drugs explored in floating dosage forms
Microspheres	Aspirin, Griseofulvin, P-nitro aniline, Ibuprofen, Ketoprofen, Terfenadine, Tranilast.
Granules	Diclofenac Sodium, Indomethacin, Prednisolone.
Films	Cinnarizine, Drug delivery device.
Powders	Several Basic Drugs.
Capsules	Chlordiazepoxide HCl, Diazepam, Furocemide, L-Dopa and Benserazide, Misoprostol, Nicardipine, Propranolol HCl, Ursodeoxychoric acid.
Tablets/Pills	Acetaminophen, Aspirin, Amoxycillin trihydrate, Ampicillin, Atenolol, Captopril, Ciprofolxacin, Chlorpheniramine maleate, Cinnarizine, Furosemide, 5-Fluorouracil, Isosorbide mononitrate, Diltiazem, Isosorbide dinitrate, Nimodipine, Para amino benzoic acid, Piretenide, Pentoxyfillin, Prednisolone, Quinidine, Varapamil HCl, Riboflavin, Sotalol, Theophyllin.

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Commercial floating formulations [34]

Name	Type and Drug	Remarks
MadoparHBS® (PropalHBS)	Floating capsule, Levodopa and benserazide	Floating CR capsules
Valrelease®	Floating capsule, Diazepam	Floating Capsules
Topalkan®	Floating Antacid, aluminum and magnesium mixture	Effervescent floating liquid alginate preparation
Amalgate Float Coat®	Floating antacid Floating gel	Floating dosage form
Conviron	Ferrous sulphate	Colloidal gel forming FDDS
Cifran OD®	Ciprofloxacine (1 gm)	Gas generating floating form
Cytotech®	Misoprostol (100 mcg/200 mcg)	Bilayer floating capsule
Liquid Gaviscone®	Mixture of alginate	Suppress gastro esophageal reflux and alleviate the heart burn

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