WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A New Approach to Prolong Gastric Retention: Floating Drug Delivery System

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ABSTRACT

The main objective of this article on the floating drug delivery system (FDDS) is to arrange current research on the role that flotation plays in achieving gastric retention. The two methods used to create FDDS by developing tablets that float, both effervescent and non-effervescent, and are supported by a buoyancy mechanism. FDDS is a drug delivery system that has a narrow window for absorption in the upper gastrointestinal tract, instability in the lower intestine environment, and low solubility at higher pH values. Some of the unique techniques in FDDS include the use of recently developed and designed polymers and variations in the formulation and physiological factors that impact stomach retention. Regarding the operation and use of floating systems, this review also emphasizes various in vitro and in vivo techniques. Traditional dose forms, such as pills or capsules, can be used with floating dosage forms. by adding the appropriate chemicals along with the gas-generating agent. Along with new and creative advancements, this study also covers several techniques for producing floating dosage forms.

Keywords: Floating drug delivery systems, Gastric retention, Effervescent, Non effervescent, Raft forming system

INTRODUCTION

Floating drug delivery systems (FDDS) were created to keep medications in the stomach. Drugs with low intestinal fluid solubility and stability can benefit from these systems. By making the dose form less dense than the stomach contents, it can float on them, which is the guiding idea of FDDS. With sufficient buoyancy to float over the contents of the stomach and remain buoyant there without materially altering the process of gastric emptying, FDDS are hydrodynamically regulated low-density devices. The drug's release causes the stomach's residual system to empty. As a result, the medication remains in the stomach for a longer period and the fluctuations in plasma drug concentration are better managed. To maintain drugs in the stomach, floating drug delivery systems, or FDDS, were developed. These methods can be beneficial for drugs with limited intestinal fluid solubility and stability. The dosage form can float over the stomach contents since it is less thick than the contents of the stomach, which is FDDS's central concept. FDDS are hydrodynamically regulated low-density devices with enough buoyancy to float above the contents of the stomach and stay buoyant there without significantly changing the process of gastric emptying. The residual system of the stomach empties as the medication is released. As a result, the medicine stays in the stomach for a longer amount of time and the variations in plasma drug concentration are more effectively controlled. Additionally, some medications show increased absorption in the gastrointestinal tract's proximal region. Furthermore, persistent drug distribution to the stomach and proximal small intestine is made possible by extending the gastric retention of the therapeutic component. intestine in the management of some ulcerative disorders. Improved bioavailability and therapeutic efficacy with fewer doses required are just two advantages of this [2]. FDDS is classified according to its physiochemical behavior and appearance, as depicted in Fig. 1.

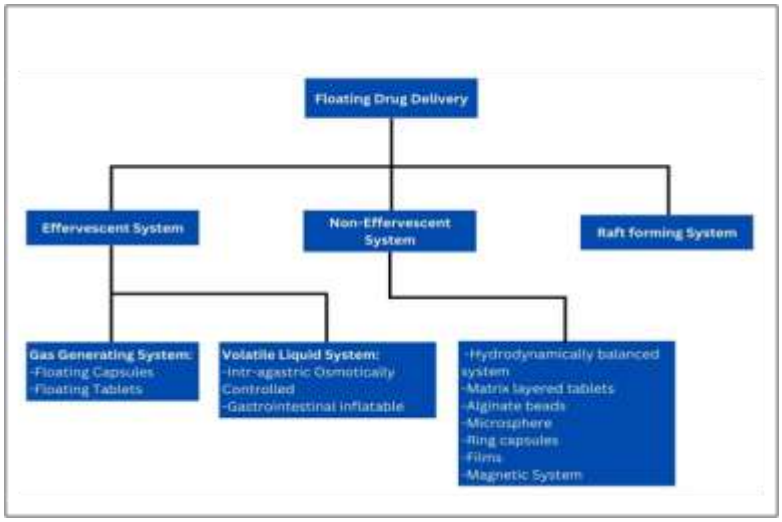

Fig.1: Classification of Floating drug delivery system (FDDS)

THE MANY BENEFITS OF FLOATING DELIVERY SYSTEMS

Floating dose systems are drug delivery strategies that behave like stomach retention and have several advantages, some of which are listed below:

1) Simple and classic formulation procedure.
2) Targeted drug delivery.
3) Managed medication delivery
4) Medication administered to a particular stomach area to ensure persistent effects.
5) Enhanced medication absorption by increased GRT and longer contact with the dosing regimen's target site.
6) Diminishing the impact of slow-releasing pharmaceuticals on the gastrointestinal tract mucosa.
7) Since aspirin and other acidic pharmacological compounds irritate the stomach mucosa when they come into contact, this formulation would be helpful when administering aspirin and other similar
8) drugs. When prolonged-release floating dosage forms, like tablets or capsules, are given, the drug dissolves in the stomach fluid and disintegrates in the gastric fluid before being absorbed in the small intestine with the emptying of the stomach's contents. As a result, it is expected that a drug in floating dosage forms will be fully absorbed if it is still in solution form even at the colon's alkaline PH.
9) Rapid intestinal motility and a brief transit time owing to a particular form of diarrhea are indicators of poor absorption. Preserving the medication in a floating state in the stomach is beneficial for increased efficacy under such conditions.
10) Greater patient compliance with simplicity of administration. In addition, there are several drawbacks to the floating medication delivery system that limit its application.

FLOATING DRUG DELIVERY SYSTEM LIMITATIONS

1. One of the main disadvantages of a floating system is that it requires a sufficient amount of gastric juices to float without a sink. To get over this restriction, the dosage form can be coated with bio-adhesive polymers that adhere to the gastrointestinal mucosa very quickly.
2. The stomach mucosal linings may get irritated by certain medications in the floating system.
3. The occurrence of gastric emptying in floating systems is highly dependent on its dimensions and can occur randomly. Therefore, patients ought not to take their prescriptions right before bed.
4. FDDS must be given after a meal; nevertheless, the condition of the digestive tract affects both the drug's residence and its emptying time, which in turn affects absorption.
5. The dosage form's capacity to float is dependent on its degree of hydration. Water must be given intermittently (one tumbler full every two hours) in order to keep these tablets floating in vivo.
6. Drugs could float in the stomach depending on how the individual is positioned.

7. Medication that is not well suited for FDDS is one that has problems with stability or solubility in stomach fluid.
8. Certain medications, such as nifedipine, should not be administered even if they effectively complete first-pass metabolism in the stomach since they may have a lower systemic bioavailability [4,6, 7].

The characteristics of a conventional vs a floating drug delivery system are displayed in Table 1. [3–4]

Table 1: Conventional Vs Floating Drug Delivery System

Parameters	**Conventional drug delivery system**	**Floating drug delivery system**
Toxicity	High risk of toxicity	Very low risk of toxicity
Patient compliance	Low	Improved
Drugs with poor solubility and high pH	Not suitable for delivery of drugs with narrow absorption window in the small intestine region	Suitable for delivery of drugs with a narrow absorption window in the small intestine region.
Drugs acting locally in the stomach	Not much advantageous for drugs having rapid absorption through GIT	Very much advantageous of drugs acting locally in the stomach.
Dose dumping	No risk of dose dumping.	Possibility of dose dumping

PHYSIOLOGICAL ELEMENTS

A multitude of physiological factors, such as pH, stomach enzymes, the kind and amount of gastric secretions, residence duration, and the effective absorbing surface area at the site of administration, have a significant impact on the administration and absorption of medications. The stomach pH, which is influenced by a number of factors such as food, illness, gasses, fatty acids, and other fermentation products, frequently affects the effectiveness of medications taken orally. Radio telemetry has been used to measure the pH of the human stomach with success. The average stomach pH in fed 1.1+0.15 is the reported mean stomach pH in fasting healthy subjects, while the situation in male healthy subjects is 3.6+0.4. This pH returns to its initial level in two to four hours. After sick situations, age is the second factor that influences gastric pH. Twenty percent of elderly people with either hypochlorhydria (decreased stomach acid production) or achlorhydria (no stomach acid secretion) had a basal pH of greater than 5.0. The syndromes of AIDS and pernicious anemia cause a significant decrease in stomach acid output as well as a high pH in the stomach.

When used orally, proton pump inhibitors and H2 receptor antagonists significantly reduce the production of stomach acid. The mean pH of the duodenum and small intestine in fasting healthy subjects was observed to be 5.8+0.3 and 6.0+0.14, respectively. The average gastrointestinal duration is five minutes to two hours. Regarding the fed and fasted situations of the stomach, two distinct patterns of gastrointestinal motility and secretions have been investigated. Migrating myoelectric complexes (MMCs), cyclic contractile events, are a type of electrical activity seen in the gastrointestinal system during fasting [5].

The following are the four stages of MMC activity:

Phase I: the period of non-contraction (30 to 60 min)

Phase II: 20–40 minutes of sporadic contractions

Phase III: consistent contractions occurring as frequently as possible (10 to 20 min)

Phase IV: transitional period between stages III and I. 0–5 minutes.

Feeding induces a three- to four-hour period of irregular contractile activity, as feeding delays these cycles. Consequently, frequent feeding increases the duration of stomach residency. Another crucial factor that greatly affects stomach emptying is the calorie level of the meals. Lyophilized and fatty contents empty more slowly than other contents. Gastric emptying is also significantly slowed down by acidity and osmolality. Stress affects gastric emptying rate, but depression decreases it. Elderly individuals and women generally empty their stomachs more slowly than do men and younger people. The rate at which the stomach empties is also affected by posture and exercise. In addition to these physiological limitations, other factors that also significantly impact stomach emptying include the size and density of the dosage form. Dosage forms with lower densities than gastric fluid exhibit floating behavior and stomach retention. It takes 1.0 gm/cm3 of density to produce the floating phenomena. Dosage forms larger than 7.5 mm in diameter show evidence of a longer stomach residence duration [5].

SELECTION GUIDE FOR USING THE FLOATING DRUG DELIVERY SYSTEM:

1) Easily absorbed in the upper gastrointestinal tract.
2) Low pKa medicines that feature unionized properties.
3) Drugs having decreased solubility at increasing pH.
4) One example of how medications work locally is the treatment of Helicobacter pylori in ulcerative illnesses.

5) Making gastro-retentive versions of medications can boost their bioavailability if they are vulnerable to breaking down in an alkaline pH environment.

6) Minimizing gastric irritation since it may increase the amount of medication concentrated in the stomach. [6, 7]

DRUG DELIVERY SYSTEM IMPLEMENTATION

1) It is stated that FDDS improves medicine efficacy because recent research show that giving Diltiazem floating tablets twice day would be more effective than giving conventional tablets to hypertensive patients.

2) FDDS is successful in preserving an adequate plasma concentration while allowing the medication to be absorbed over a period of 6 to 8 hours in Parkinson patients.

3) Drugs that are specifically absorbed from the stomach or the proximal portion of the small intestine, such as furosemide and riboflavin, benefit greatly from site-specific drug delivery systems, or FDDS.

4) The use of FDDS was an effective drug delivery system for the eradication of Helicobacter pylori, the causative agent of peptic ulcers and chronic gastritis.

5) The best hydrodynamically balanced system (HBS) for optimal drug delivery and less GI side effects is FDDS. [8–6]

The following polymers are examples of how floating drug delivery systems are made: polyvinyl acetate; gel of polyacrylate, HPMC, and chitosan; EudragitS100; Eudragit; HPMC; HPMC-Guar gum combination; HPMC-Locust bean gum combination; Sodium alginate beads; EC-HPM combination.

The categorization of floating drug delivery systems

(A) Floating medication delivery device that works effectively

These specialized drug delivery systems are composed of polymers that can swell, such as chitosan and methylcellulose, as well as effervescent chemicals, such as citric acid, tartaric acid, and sodium bicarbonate. They are made in a way that releases CO2 upon contact with stomach fluid and traps it in an expanding hydrocolloid, giving the dose form buoyancy. The basis of this delivery technique is the swellable asymmetric triple layer tablet approach[22–24].

(I) Systems that produce gasss

Low-density FDDS is predicated on the interaction of oral administration with stomach fluids and subsequent CO2 release. The materials are made in such a way that, once entering the stomach, they react with the acidic gastric contents to produce CO2, which is then trapped in the gel-based hydrocolloid (fig.2). It keeps the dose form buoyant and causes it to rise. Eventually, it causes the dose form's specific gravity to decrease, which causes a float to appear on the chime. One way to generate CO2 is to combine the components that produce it in a single layer or in many layers within the tablet matrix's hydrocolloid layer [22, 25]. This method will produce gas. And from the other layer, the medicine is released gradually over a longer duration.

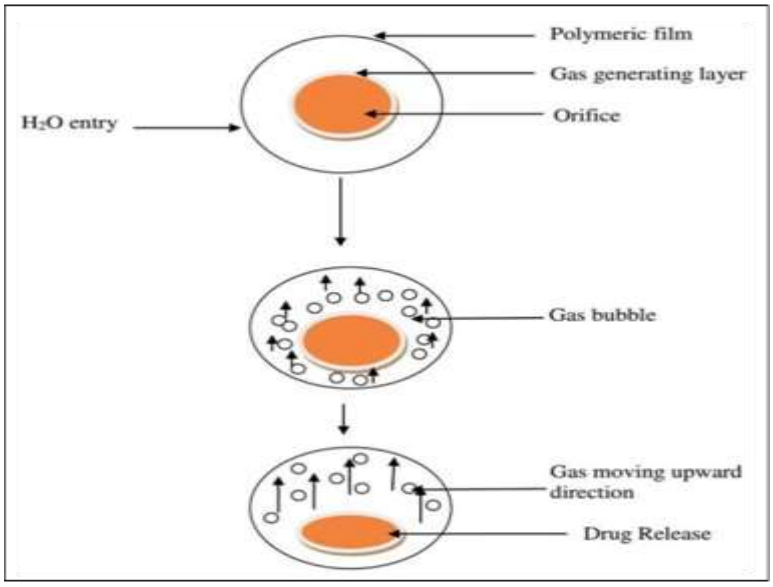

Fig. 2: A floating mechanism that releases CO2

(II) Osmotically regulated drug delivery systems, or volatile liquid systems

This osmotically controlled floating system consists of a device composed of a hollow deformable unit in convertible compressed condition. Attached to its deformable unit, the housing would be internally divided into a first and second chamber, divided further by an impermeable, pressure-sensitive movable unit. The drug reservoir is made to float by vaporizing a volatile liquid, like cyclopentane or ether, at a physiological temperature in the second chamber. Usually, an active medication is found in the first chamber. It is expelled from the stomach by means of a bioerodible stopper that permits the vapor to escape [22, 25].

(B) Non-effervescent FDDS

Gel-forming (or swellable) cellulose hydrocolloids and matrix-forming polymers such as polycarbonate, polymethacrylate, and polystyrene are examples of non-efflorescent floating drug delivery systems. The conventional approach to drug formulation involves mixing the medication with hydrocolloids, which gel when taken orally and maintain their shape and bulk density barrier; the air trapped by the expanding polymer gives the dosage forms their buoyancy [22, 25].

(I) Systems balanced by hydrodynamics

By using this strategy, the amount of medicine that is sent to the absorption site in solution form is increased, and the length of gastric retention is prolonged. It consists primarily of medications containing hydrocolloids that gel in the stomach. Such a system includes one or more hydrocolloids of the cellulose type that gel, including hydroxypropylmethylcellulose (HPMC), as well as polysaccharides and matrix-forming polymers like polycarbophil, polystyrene, and polyacrylate. When the system's hydrocolloid comes into contact with GI fluid, it hydrates to form a colloid gel barrier to its environment [22, 25].

(II) Systems of microporous compartments

This technique surrounds a drug reservoir inside a microporous compartment and has pores on both the top and bottom sides. The drug reservoir compartment's peripheral wall is completely sealed to prevent any direct contact between the undissolved drug and the stomach surface. Because of the air-filled floating chamber, the delivery system floats over the gastric contents of the stomach. Gastric fluid enters through the opening to convey the dissolved medicine for further transportation across the gut for absorption and to prevent escape from the drug [25].

(III) Microspheres in Float

It is believed that the most efficient buoyant system is made up of hollow microspheres, also called micro balloons. It consists of the hollow center of the microsphere. An unusual one

dissolver Diffusion method for emulsion is utilized to make hollow microspheres that are loaded with a medicine in their outer polymer shelf [24].

IV) Beads of alginate

Multi-unit floating dosage forms have been created using spherical beads made of calcium alginate, measuring around 2.5 mm in diameter. To make these beads, dissolve a solution of sodium alginate in an aqueous solution of calcium chloride, causing the calcium alginate to precipitate. In order to generate a porous system, the beads are then separated, snap-frozen in liquid nitrogen, then freeze-dried for 24 hours at 400 °C. The floating force would be maintained by this artificial system for more than 12 hours, and the floating beads offer a longer residence period of more than 5.5 hours [25].

(C) Systems for building rafts

Raft-forming systems are getting a lot of attention for the administration of antacids and medications

for gastro-infection and illnesses. When a gel-forming solution comes into contact with stomach fluid, it swells and forms a cohesive, thick gel that is trapped with CO2 bubbles. This raft layer forms on top of the gastric fluid and facilitates the drug's gradual release in the stomach [25].

THE FACTORS INFLUENCING THE INTESTINAL WALL THE FLOATING DRUG DELIVERY SYSTEM'S TIME

A) Elasticity parameters

Tablet dimensions

The floating retention phenomena of dose forms in the stomach is mostly caused by the size of the pills. During the digestion process, smaller tablets get through the stomach more rapidly than larger ones.

Tablet density

Another factor that influences the length of time a dose form remains in the stomach is density. Given its adequate distance from the pyloric sphincter, a buoyant dosage consisting of a density reduced than the gastric fluids would float and cause the stomach to retain more food for a longer period of time. It has been discovered that tablets with a density of 1.0 g/ml or less—which are generally believed to be less dense than stomach contents—are more

effective. On the other hand, the floating force kinetics has shown that the bulk density of a dose form is not the main factor affecting its buoyancy characteristics.

Tablet shape

Since the shape of the dose form influences the stomach residence period, it is also considered one of the contributing factors. The in vivo retention of six different types of forms—ring tetrahedron, cloverleaf, string, pellet, and disk—is evaluated. During a 24-hour period, the tetrahedron-shaped rings in this study, with each leg measuring 2 cm, retained nearly all of their information.

The viscosity of polymers

FDDS floating characteristics and drug release are significantly influenced by the viscosity of different grades of polymers and their interactions. Low viscosity polymers (such HPMC K100 LV) have been demonstrated to increase the dosage form's floating properties better than high viscosity polymers (like HPMC K4M). Furthermore, a drop in the release rate was found to correlate with an increase in polymer viscosity.

B) Anomalous variables

Gender

A study found that women's stomach emptying times are longer than men's. Men had a shorter mean ambulatory stomach retention time (3.4+0.4 h) than their age- and race-matched female counterparts (4.6+1.2 h), regardless of weight, height, or body surface.

Age

Additionally, older adults have faster gastric emptying times than younger adults. There may be differences in the transit periods of the intestines and stomach between individuals. The typical duration of stomach retention is significantly longer in the elderly, particularly in those over 70.

Position: straight

Postprandial emptying is delayed because the floating shape, no matter how big, remains above the stomach contents [13]. Floating dose forms have more consistent and prolonged gastric retention durations than conventional dosage forms, which tend to sink towards the bottom of the distal stomach from whence they are expelled by peristaltic movements through the pylorus.

Posture: prone position

Against erratic and premature emptying, this approach offers no reliable resistance. Patients who are supine may retain large dosage forms (both floating and conventional) longer. The stomach's lesser and greater curvatures appear to have no effect on the gastric retention of floating forms. The distal movement of these units may be swept away by the peristaltic motions that push the stomach contents towards the pylorus. This would lead to a significant decrease in the gastric retention duration in comparison to the participants who stood upright.

Concurrent drug consumption

Numerous medicines taken concurrently may affect the floating drug delivery system's function, including opiates (like codeine), prokinetic agents (like metoclopramide and cisapride), and anticholinergics (like atropine or propantheline). When GI motility-decreasing medications are concurrently used, the duration of gastric emptying may be extended, and vice versa.

Feeding schedule.

Food lengthens the gastric residence time, which speeds up the pace at which the dosage form dissolves the medicine at the absorption site of choice. Stomach retention has been reported for four to ten hours after a diet heavy in lipids and proteins [26–28].

THE PHARMACOLOGICAL AND PHARMACODYNAMIC PROPERTIES OF FDDS

Enhanced bioavailability.

FDDS has looked into ways to increase the bioavailability of a few medications having a narrow therapeutic window due to poor GI absorption brought on by a variety of factors that also contribute to lower bioavailability. Although the medications under consideration had a restricted absorption window, FDDS showed promise for increased compound bioavailability at the necessary location. The bioavailability of levodopa and riboflavin in control release (CR) floating devices is significantly higher than when administered in the standard formulation. Alendronate and other bisphosphonates, on the other hand, are quickly absorbed from the stomach when used with CR polymeric products. The amplitude of this pathway is still rather small even when experimental or surgical procedures are the reason for the rats' prolonged stomach retention of the bisphosphonate. Conclusion: Multiple mechanisms related to drug absorption and transit in the gastrointestinal tract work simultaneously and impact the extent of drug absorption.

Enhanced first-pass biotransformation efficiency

If the drug is administered to the metabolic enzymes (cytochrome P450, specifically CYP3A4) gradually rather than all at once, as is the case with bolus inputs, the pre-systemic metabolism of the tested compound has a markedly increased cause of FDDS, comparable to the enhanced efficacy of limited capacity active transporters.

Bioavailability is increased when P-glycoprotein (P-gp) activity in the duodenum is reduced.

In apparent opposition to the increased density of CYP3A4 in the upper region of the intestine, P-gp mRNA levels climb longitudinally along the gut, peaking in the colon. Therefore, for medications like Digoxin that are P-gp substrates and do not experience oxidative metabolism, floating systems may result in increased absorption as compared to immediate and controlled release (CR) dose forms.

Decreased frequency of dosing

Pharmacokinetics of pharmaceuticals with relatively short biological half-lives, slow input from continuous release, and control release floating system flip-flops have been seen, according to the findings of multiple studies. This quality makes patients more compliant, which improves treatment.

Specific therapy for disorders of the upper gastrointestinal tract.

Prolonged and sustained drug administration from the floating systems to the stomach may be beneficial for local therapy in the stomach and small intestine.

ASPECTS OF FDDS PHARMACODYNAMICS

Decreased variations in medication concentration

When the floating method of drug administration is used instead of immediate release dosage forms with continuous drug input, the blood drug concentrations are more consistent within a narrower range. As a result, pharmacological effects fluctuate as little as possible, and undesirable effects that depend on concentration and are linked to peak concentrations can be avoided. This feature is especially beneficial for medications with a low therapeutic index.

Enhanced selectivity of receptor activation

By reducing changes in drug concentration, it is also possible to obtain some selectivity in the induced pharmacological activity of medications that activate different types of receptors at different doses.

Reduced counteractivity of the body

The pharmacological response frequently results in a rebound activity that lessens the benefits of the

medicine by interfering with the body's regular physiological processes. Research has shown that pharmacological effectiveness is increased and counteractivity is decreased when drugs are absorbed slowly, as in the case of FDDS.

Decreased negative colonic activity

When the medication is kept in the FDDS, especially in the stomach in the gastro retentive form, less of it enters the colon. Consequently, the adverse effects of the medication on the colon might be prevented. This pharmacologic characteristic explains the floating formulation of beta-lactam antibiotics, which are only absorbed from the small intestine and whose presence in the colon causes the multiplication of bacteria [31].

CONCLUSION

Drug absorption takes longer when the dose form is kept in the stomach longer. The gastrointestinal tract's process of absorbing drugs is very diverse. With FDDS, gastric retention might be possible to treat. As evidence, these industries have a large number of registered patents and marketable goods. Increasing the drug's bioavailability in the gastrointestinal tract—a location with a narrow window for absorption—is the aim.

By spending more time in the GI tract, drugs that are less soluble at high pH can become more soluble while also reducing drug waste and variations in plasma levels. Even though there are still a lot of problems that need to be fixed before sustained gastric retention can be achieved, many companies are trying to commercialize this method

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