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A Review on Floating Drug Delivery System

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Abstract: *The floating drug delivery system (FDDS) enhances the buoyancy of pharmaceuticals within gastric fluids, thereby prolonging their therapeutic effects. This system is advantageous in reducing the frequency of dosing. For an effective FDDS, the density of the dosage form must be lower than that of gastric contents, which is approximately 1.004 gm/ml. FDDS can be categorized into effervescent and non-effervescent systems. Drugs that exhibit a narrow absorption window in the gastrointestinal tract are particularly suitable for this delivery method. The primary aim of this review article is to consolidate recent findings, emphasizing the physiology of stomach, classification, preparation techniques, mechanisms of action, as well as the associated benefits and drawbacks.*

Keywords: Floating drug delivery systems, Gastro-retentive drug delivery system, GIT physiology

I. INTRODUCTION

Oral drug administration is the most versatile, convenient, and commonly used method for delivering drugs systemically. The oral route of administration has gained significant attention and success in the development of controlled release systems due to the flexibility it offers in dosage form design, particularly in gastrointestinal physiology. Among the various methods of oral drug administration, floating drug delivery has garnered attention from researchers for delivering drugs that are highly soluble in acidic environments and those that are unstable in alkaline environments. The concept of floating drug delivery systems (FDDS) was first introduced in 1968 by Davis, who developed a method to address the difficulty experienced by individuals when swallowing medicinal pills. FDDS are low-density systems designed to float over gastric contents and remain in the stomach for an extended period, offering economic benefits, improved patient compliance, and advantages for drugs absorbed from the stomach. Gastroretentive drug delivery systems are specifically designed to remain in the stomach for a prolonged period, releasing their active ingredients and providing sustained drug input to the upper gastrointestinal tract. A modified release drug delivery system with prolonged residence time in the stomach is particularly beneficial for drugs that act locally in the stomach, have an absorption window in the stomach or upper small intestine, are unstable in intestinal or colonic environments, or have low solubility at high pH values.Various methods are employed in the development of an effective gastroprotective drug delivery system, including floating drug delivery system, low density systems, raft systems with alginate gel, bioadhesive or mucoadhesive systems, high density systems, superporous hydrogel, and magnetic system. Floating dosage forms, in particular, have emerged as the most widely utilized approach. These forms can be produced as tablets or capsules through the incorporation of suitable excipients and gas-generating agents, enabling the dosage form to float in gastrointestinal fluids.

DEFINITION

Floating systems are characterized by their low density, allowing them to float on the stomach and remain buoyant in the gastric environment without impacting the rate of gastric emptying over an extended period. As the system floats within the gastric contents, the drug is gradually released at the desired concentration, facilitating the clearance of residue from the stomach. These outcomes contribute to the elevation of gastric residence time (GRT) and improved control over plasma drug concentrations. Additionally, floating systems are beneficial for delivering local drugs to the proximal gastrointestinal tracts, such as antibiotics for Helicobacter pylori in the management of peptic ulcers, as well as for drugs that are challenging to dissolve or are unstable in intestinal fluids.

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Physiology of GIT

The stomach is anatomically categorized into three distinct regions: the Fundus, Body, and Antrum (pylorus). The proximal section, which includes the fundus and body, functions primarily as a storage area for undigested food, whereas the antrum is engaged in mixing movements and operates as a pump to facilitate gastric emptying through its propulsive actions. Gastric emptying takes place during both fasting and fed conditions. During fasting, a sequence of interdigestive electrical activities occurs cyclically within the stomach and intestines approximately every 2-3 hours. This sequence is referred to as the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which can be further subdivided into four distinct phases.

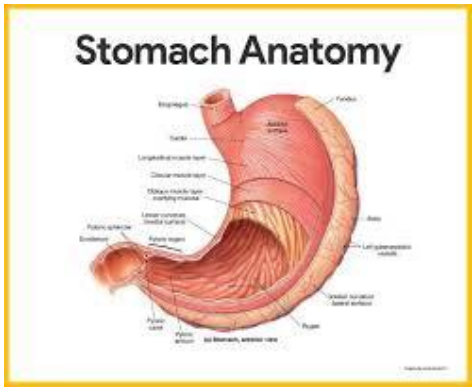

Fig.1: Physiology of GIT

Gastrointestinal Motility Pattern

1. Phase 1, often referred to as the basic phase, has a duration of 30 to 60 minutes and is marked by infrequent contractions.
2. Phase 2, known as the preburst phase, follows and lasts for 20 to 40 minutes, during which intermittent action potentials and contractions occur.
3. Phase 3, identified as the burst phase, is characterized by a duration of 10 to 20 minutes and features intense, regular contractions over a brief period.
4. Phase 4 occurs for a duration of 0 to 5 minutes, situated between phases 2 and 1 in two consecutive cycles.

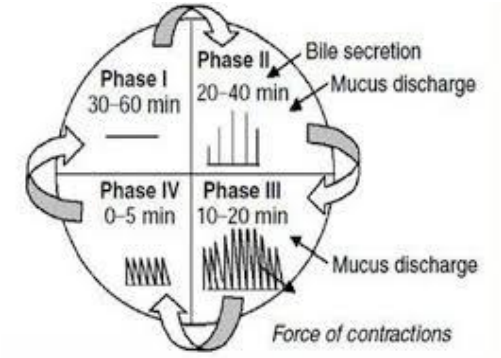

Fig.2: Gastrointestinal motility pattern

After the intake of a diverse meal, the pattern of contractions transitions from a fasted state to a fed state, which is typically described as the digestive motility pattern.

II. CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

A. Single Unit Floating Dosage Systems

a) Effervescent Systems (Gas-generating Systems)

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b) Non-effervescent Systems

B. Multiple Unit Floating Dosage System

a) Effervescent Systems (Gas-generating Systems)
b) Non-effervescent Systems
c) Hollow Microspheres

C. Raft Forming System

A. Single Unit Floating Dosage Systems

a. Effervescent Systems (Gas-generating Systems)

The phenomenon of floatability can be facilitated through the production of gas bubbles. The generation of carbon dioxide (CO2) can occur in situ by the introduction of carbonates or bicarbonates, which undergo a reaction with acid, whether it be the naturally occurring gastric acid or acids such as citric or tartaric acid that are co-formulated. Research indicates that the optimal stoichiometric ratio for the generation of gas between citric acid and sodium bicarbonate is approximately 0.76:1. The gastric floating drug delivery system (GFDDS) presents several advantages compared to alternative gastric retention systems. These systems possess a bulk density that is lower than that of gastric fluids, allowing them to remain buoyant within the stomach without influencing the gastric emptying rate over an extended duration. While the system remains afloat amidst the gastric contents, the drug is released gradually at a predetermined rate from the stomach.

Non-effervescent Systems

These dosage forms are characterized as single-unit systems that incorporate one or more gel-forming hydrophilic polymers. Among these, hydroxypropylmethylcellulose (HPMC) is the most prevalent excipient utilized; however, alternatives such as ethylcellulose (HEC), hydroxypropylcellulose (HPC), sodium carboxymethyl agar, carrageenan, and alginic acid are also employed. The polymer is combined with the active pharmaceutical ingredient and is typically delivered in a gelatin capsule. Upon administration, the capsule swiftly dissolves in gastric fluids, leading to the hydration and swelling of the surface polymers, which results in the formation of a floating mass. The release of the drug is regulated by the establishment of a hydrated boundary at the surface. The ongoing erosion of this surface facilitates the ingress of water into the inner layers, thereby sustaining surface hydration and buoyancy. The addition of fatty excipients contributes to the creation of low-density formulations, which in turn diminishes water penetration and slows down erosion. The efficacy of drug delivery is contingent upon the optimal balance between drug loading and the influence of the polymer on the drug's release characteristics.

B. Multiple Unit Floating Dosage Systems

The utilization of multiple unit dosage forms presents a promising alternative, as research indicates a decrease in both inter- and intra-subject variability in drug absorption, alongside a diminished risk of dose dumping. Various multiple unit floating drug delivery systems (FDDS) have been developed, employing strategies such as systems comprising multiple air compartments, hollow microspheres fabricated through the emulsion solvent diffusion technique, and beads produced via the emulsion gelation method. Additionally, the incorporation of effervescent and swellable polymers represents another innovative approach in the design of multiple unit FDDS.

a. Effervescent Systems

A multi-unit system was developed, featuring a core of calcium alginate and a membrane composed of calcium alginate and PVA, with an intervening air compartment. The presence of water facilitates the leaching of PVA, which enhances the membrane's permeability while maintaining the integrity of the air compartment. An increase in both the molecular weight and concentration of PVA has led to improved floating characteristics of the system. Additionally, the method of freeze-drying is utilized for the fabrication of floating calcium alginate beads. In this process, a sodium alginate solution is introduced dropwise into a calcium chloride aqueous solution, resulting in immediate gelling of the droplet surface. The resulting beads undergo freeze-drying, which creates a porous structure conducive to buoyancy. The

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researchers investigated the behavior of radiolabelled floating beads, employing gamma scintigraphy to compare them with non-floating beads in human subjects. The floating beads demonstrated a significantly prolonged gastric residence time, exceeding 5.5 hours, whereas the non-floating beads exhibited a shorter residence time with an overall emptying duration of 1 hour.

b. Non-effervescent Systems

In contrast with the effervescent systems, there was not much study on effervescent multiple unit systems found in the literature. Few workers, however, have documented the possibility of creating such an indomethacin-containing method, using chitosan as the polymeric excipient. A multiple HBS unit containing indomethacin is recorded as a model drug prepared by the extrusion process. Via the blade, a mixture of drug, acetic acid and chitosan, is extruded and the extrudate is cut and dried. In the acidic media, chitosan hydrates and floats, the requisite drug release could be achieved by changing the ratio of drug-polymer.

c. Hollow Micro spheres

Hollow microspheres containing drugs were synthesized utilizing an innovative emulsion solvent diffusion technique within their outer polymeric layer. A solution of the drug in ethanol and dichloromethane, along with an enteric acrylic polymer, was introduced into a thermally regulated, agitated solution of Poly Vinyl Alcohol (PVA) at 40°C. The evaporation of dichloromethane led to the formation of a gas phase within the dispersed polymer droplet and the hollow cavity of the drug-loaded microsphere. These micro-balloons exhibited sustained buoyancy, remaining afloat on the surface of an acidic dissolution medium containing surfactants for over 12 hours. The hollow microspheres represent a highly promising class of buoyant structures due to their internal hollow space, which confers unique advantages akin to various unit systems, as well as improved floating properties.

C. Raft Forming System

Raft-forming systems have garnered significant interest for their application in delivering antacids and medications targeting gastrointestinal infections and disorders. The underlying mechanism of raft formation involves the creation of a viscous, cohesive gel upon contact with gastric fluids. In this process, each segment of the liquid expands, resulting in the development of a continuous layer known as a raft. This raft remains buoyant on gastric fluids due to the low bulk density generated by the production of carbon dioxide (CO_2). Typically, these systems incorporate a gel-forming agent along with alkaline bicarbonates or carbonates, which facilitate CO_2 generation, thereby reducing density and enabling flotation on gastric fluids. An example of such a raft-forming floating system includes a combination of a gel-forming agent (such as alginic bicarbonate, calcium carbonate, mannitol) and a sweetener. These components are granulated, with citric acid subsequently added to the mixture. This formulation induces effervescence, enhancing the aeration of the raft and promoting its flotation. The presence of sodium bicarbonate and an acid neutralizer leads to the formation of a foaming sodium alginate gel (raft) upon interaction with gastric fluids. The resultant raft serves as a barrier, floating on gastric fluids and preventing the reflux of gastric contents, including gastric acid, into the esophagus. A patent held by Reckitt and Colman Products Ltd. details a raft-forming formulation specifically designed for the treatment of Helicobacter pylori (H. pylori) infections within the gastrointestinal tract.

III. ADVANTAGES

Floating dosage systems represent a category of drug delivery mechanisms characterized by their ability to remain buoyant within the gastric environment. These systems provide numerous benefits in the realm of pharmacotherapy. Among these advantages are:

1. A straightforward and traditional method for drug formulation.
2. Targeted drug delivery to specific sites.
3. Regulated release of pharmaceuticals.
4. Administration of medications for sustained action at a designated location within the stomach.
5. Enhanced drug absorption through prolonged gastric residence time (GRT) and extended contact duration of the dosage form at its intended site.

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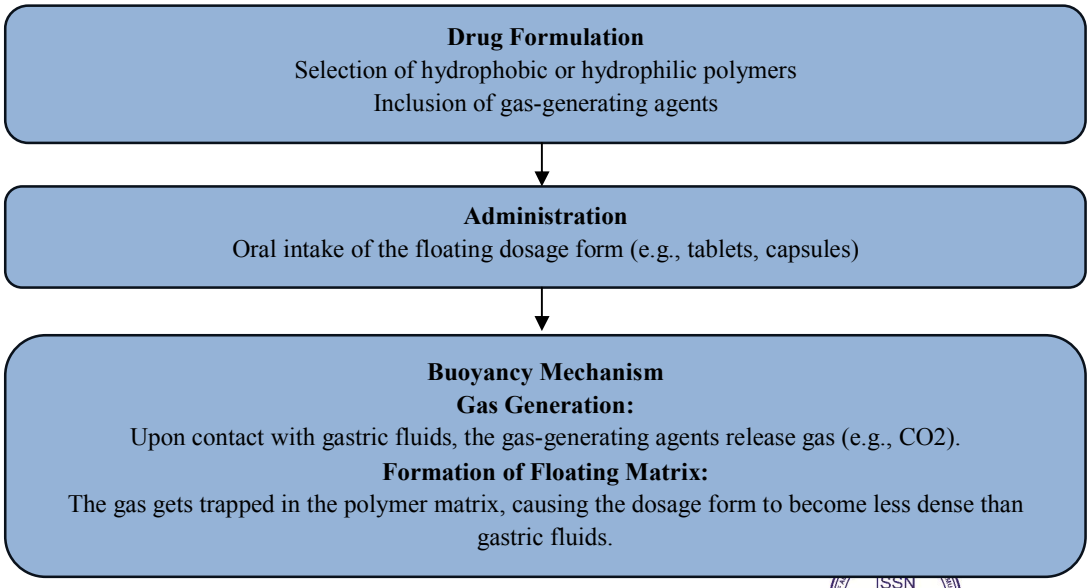
6. Reduction of gastrointestinal tract (GIT) mucosal irritation by utilizing drugs with a gradual release profile. Acidic compounds, such as aspirin, can irritate the gastric lining upon contact. Therefore, the use of hydrophilic biopolymer systems (HBS) would be advantageous for the administration of aspirin and similar agents. The prolonged release of floating dosage forms, whether in tablet or capsule form, facilitates the dissolution of the drug in gastric fluids. These formulations dissolve in the stomach before being absorbed in the small intestine, coinciding with the emptying of gastric contents. Consequently, it is anticipated that drugs will achieve complete absorption from floating dosage forms, even at the alkaline pH encountered in the intestine.
7. In instances of vigorous intestinal motility and rapid transit times, there is a potential for diarrhea, which may lead to suboptimal absorption. In such scenarios, maintaining the drug in a floating state within the stomach can enhance therapeutic efficacy.
8. In the management of gastroesophageal reflux disease (GERD).
9. Simplified administration leading to improved patient adherence.

IV. DISADVANTAGES

1. A significant drawback of floating drug delivery systems is the necessity for a sufficiently elevated level of fluids within the stomach to facilitate the buoyancy of the dosage form. This challenge can be addressed by employing bioadhesive polymers for coating the dosage form, which can effectively adhere to the gastric mucosal lining.
2. The retention of drugs in the stomach is subject to various influencing factors, including gastric motility, pH levels, and the presence of food. These variables are inherently unstable, making it difficult to predict buoyancy accurately. Drugs that induce irritation or lesions in the gastric mucosa are unsuitable for formulation as floating drug delivery systems.
3. There exists a considerable variability in gastric emptying times, which can be characterized by an all-or-nothing phenomenon.
4. It is advisable for patients to avoid taking floating dosage forms immediately before bedtime.
5. Floating drug delivery systems are impractical for medications that exhibit solubility or stability issues in gastric fluids.
6. The administration of the dosage form should be accompanied by a minimum of one full glass of water (200-250 ml).
7. Drugs that are absorbed throughout the gastrointestinal tract and undergo first-pass metabolism, such as Nifedipine and Propranolol, are not ideal candidates for floating drug delivery systems.

V. MECHANISM OF FDDS



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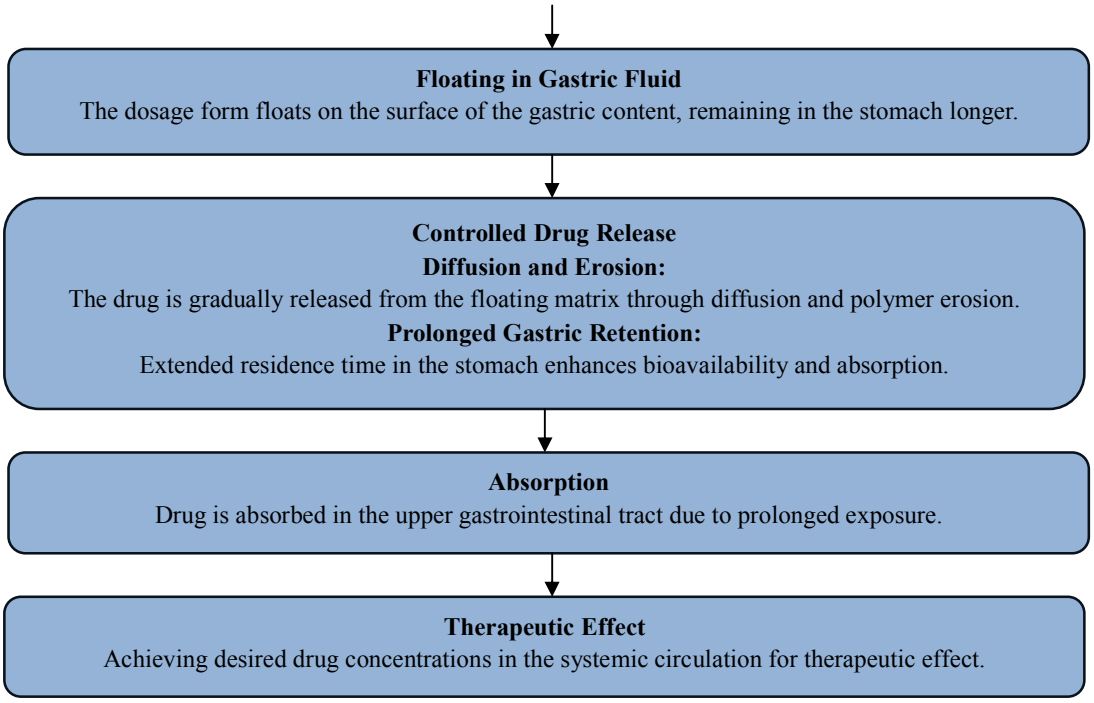

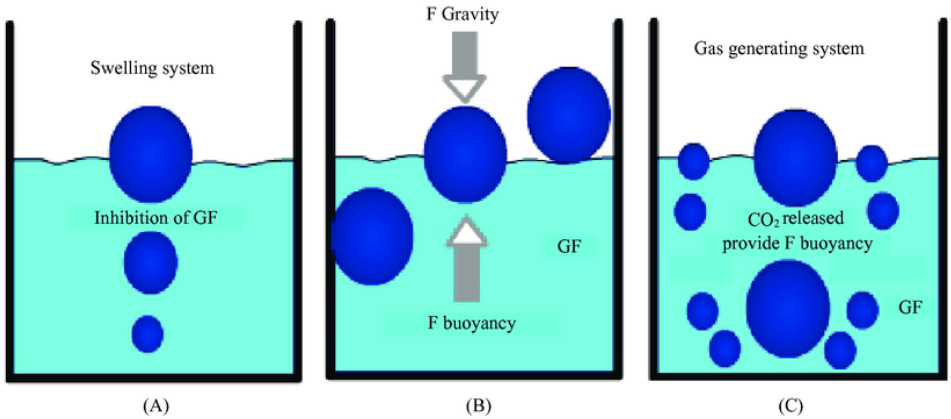

Fig.4: Mechanism of FDD

VI. APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery systems (FDDS) represent a novel approach to pharmaceutical formulation aimed at improving the bioavailability of drugs by extending their residence time in the stomach. The following are notable applications of FDDS:

- **Improved Absorption:** By remaining in the gastric environment for an extended duration, FDDS can enhance the absorption of medications that are optimally absorbed in this setting, including certain antacids, antibiotics, and antihypertensive agents.
- **Targeted Delivery:** FDDS can be specifically designed to direct drugs to particular locations within the gastrointestinal tract, which is especially beneficial for treating conditions such as peptic ulcers or localized infections.

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- **Controlled Release:** These systems facilitate a sustained release of the active pharmaceutical ingredient over a prolonged timeframe, thereby decreasing the frequency of administration and enhancing patient adherence to treatment regimens.
- **Minimization of Side Effects:** By regulating the release kinetics and maintaining drug concentrations within therapeutic ranges, FDDS can help reduce the incidence of side effects that may arise from rapid drug release.
- **Formulation of Poorly Soluble Drugs:** FDDS can improve the solubility and stability of drugs with poor solubility profiles, thereby enhancing their absorption and overall therapeutic efficacy.
- **Management of Gastric Emptying Disorders:** For individuals suffering from conditions such as gastroparesis, FDDS can offer significant advantages by accommodating irregularities in gastric emptying.
- **Enhanced Stability:** Certain drugs are prone to degradation within the gastrointestinal tract; FDDS can safeguard these compounds, ensuring their therapeutic effectiveness.
- **Oral Insulin Delivery:** Ongoing research is exploring the potential of FDDS for the oral administration of insulin, with the goal of providing a non-invasive alternative for diabetes management.
- **Applications in Herbal and Nutraceutical Delivery:** FDDS can also be employed to deliver herbal extracts and nutraceuticals, thereby improving their bioavailability and therapeutic impact.
- **Formulations for Pediatric and Geriatric Populations:** FDDS can be specifically developed to meet the unique requirements of pediatric and geriatric patients, who may encounter challenges with traditional dosage forms.

Need for a floating drug delivery system.

A specific anatomical site is required for the absorption of certain medications. These drugs necessitate a targeted release mechanism that guarantees the optimal amount of the active ingredient reaches the intended site. Currently, the pharmaceutical sector is increasingly focused on developing site-specific medications. One such method of drug delivery is gastro-retentive administration, which involves retaining the dosage form within the stomach and gradually releasing the medication to a specific area within the stomach, duodenum, or intestine.

Probable candidates for FDDS

Pharmaceuticals characterized by a limited absorptive capacity within the stomach or the proximal segments of the small intestine include compounds such as furosemide, riboflavin-5-phosphate, metformin hydrochloride, ciprofloxacin, alfuzosin hydrochloride, ofloxacin, norfloxacin, and domperidone. Additionally, certain medications exhibit instability in the distal regions of the gastrointestinal tract, exemplified by captopril. Furthermore, there are drugs that demonstrate poor solubility in intestinal fluids, such as quinidine and diazepam. Lastly, some substances, including ranitidine hydrochloride and metronidazole, are prone to degradation within the colon.

VII. CONCLUSION

The mechanism, different types of floating systems, benefits, drawbacks, factors influencing floating systems, drug candidates appropriate for floating, assessment criteria, and system application are all succinctly explained in the review. These systems can help with a number of issues that come up while developing a pharmaceutical dosage form and with the promise that FDDS has in the future.

This study outlines the benefits and potential applications of the current FDDS technology advancements for oral controlled drug delivery, including commercial products and patented delivery systems.

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