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FEATURES AND FACTS OF GASTRO RETENTIVE FLOATING DRUG DELIVERY SYSTEMS-A REVIEW

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ABSTRACT

Drugs with poor solubility and limited stability in intestinal fluids can be administered using floating drug delivery systems (FDDS), which were developed to keep the medicine in the stomach. The idea of FDDS is to create a dose form that will float on stomach fluids by making it less dense than those fluids. FDDS is a strategy for delivering medications that are unstable in the lower intestinal environment, have little solubility at higher pH levels, and are locally active with a small window of absorption in the upper gastrointestinal tract. The unique methodology in FDDS include methods for designing single- and multi-unit floating systems, methods for addressing physiological and formulation variability that affects stomach retention, and methods for utilising freshly created and produced polymers. FDDS are hydrodynamically regulated low-density systems with enough buoyancy to float over the contents of the stomach and remain buoyant there without slowing down the gastric emptying rate for a long time. Physiological and formulation variability impacting stomach retention, techniques to design single-unit and multiple-unit floating systems, and the utilisation of freshly produced and invented polymers are some examples of the unique methodology in FDDS. Floating dosage forms can be administered in traditional forms like tablets or capsules by including the gas-generating agent and the proper components. This review also discusses several methods for creating floating dosage forms, as well as recent and innovative developments.

KEYWORDS: Gastro retentive, floating drug delivery, low density, absorption window, buoyant.

INTRODUCTION

Any drug delivery system must deliver the right amount of medication to the appropriate site in the body to quickly attain and then sustain the appropriate drug concentration. Technology has recently progressed to the point that there are now viable dosage options that can be supplied in various ways. There are several different methods employed, including oral, topical, nasal, rectal, vaginal, and ophthalmic.[1] The most efficient and recommended method of delivering any medicine to systemic circulation is oral administration.[1] Due to its simplicity, patient compliance, and formulation flexibility, oral delivery is responsible for the majority of medications that are delivered. The bioavailability of medications administered via this route, however, might vary significantly, especially if the utilizing traditional or immediate-release dose forms, or medicinal drugs are administered.[2] These medications must be dosed frequently to get the desired therapeutic effect. The development of oral sustained-controlled release formulations is an effort to overcome this limitation by slowly releasing the drug into the gastrointestinal tract (GIT) and maintaining an effective drug concentration in the systemic circulation for an extended period.[3] Such a drug delivery would be remained in the stomach after oral administration and release the drug in a controlled manner, permitting the drug to be constantly given to its absorption sites in the gastrointestinal system (GIT).[4] Short gastric retention time (GRT) and unpredictable short gastric emptying time (GET) are the main drawbacks of these drug delivery systems. These drawbacks can cause incomplete drug release from the dosage form in the absorption area (stomach or upper part of small intestine), which can reduce the effectiveness of the dose that was administered.[5,6]

It is desirable to extend the drug delivery's stomach residence duration to provide an oral controlled release dosage form that is site-specific. Long-term stomach retention increases bioavailability, extends the time it takes for a drug to begin working, decreases drug waste, and increases the solubility of drugs that are less soluble in high-pH environments.[7] Several gastro-retentive drug delivery techniques have been developed during the past few decades, including high-density (sinking) systems that are retained in the. systems that prevent emptying of the dosage forms through the pyloric sphincter of the stomach, such as super porous hydrogel systems, magnetic systems, unfoldable, extensible, or swellable systems,

etc.[8-10] Designing a regulated delivery system to improve bioavailability and absorption presents several challenges. The inability to contain the dose form in the desired region of the gastrointestinal tract is one of these challenges. Drug absorption from the GIT is a complicated process that depends on numerous factors. It is generally accepted that the duration of time a drug spends in contact with the small intestinal mucosa influences how much of the gastrointestinal tract it absorbs. As a result, the small intestinal transit time is a crucial factor for medications that are only partially absorbed. Basic human physiology is discussed, including information on gastric emptying, motility patterns, and physiological and formulation factors that affect cosmic emptying. The gastric residence duration of medications is greatly extended by gastro retentive systems since they might stay in the gastric region for several hours. Increased bioavailability, decreased drug waste, and improved solubility for medications that are less soluble in high pH environments are among the benefits of prolonged stomach retention. It can be used to deliver medications locally to the stomach and proximal small intestine.[11]

Gastroretention

Maintaining the drug reservoir above its absorption area, i.e., in the stomach (gastro retention), and discharging the drug in a controllable manner are acceptable approaches to improving bioavailability, pharmacokinetic, and pharmacodynamic characteristics.[12,13] Compared to predictable dose forms, the gastroretentive dosage form stays in the stomach for a longer time. Gastric retention can be substantially prolonged by gastroretentive systems, which can remain in the gastrointestinal region for several hours. This increases bioavailability and decreases drug waste.[14]

Need For Gastroretention

1. Drugs whose absorption is erratic due to a variable stomach-emptying time
2. Due to an alkaline pH, medications that are not sufficiently soluble in the intestine may cause increased gastric retention.[14]
3. The primary function of gastro retention is to treat peptic ulcers brought on by H. pylori infections.
4. For medications whose alkaline pH causes gastrointestinal degradation, gastro retention is important.
5. Solubility before emptying them, increasing bioavailability

6. Additionally, it is crucial for medications like antacids that should operate locally in the stomach.[15]

Advantages of Gastroretentive Delivery System

1. The gastrointestinal absorption of medications with limited absorption windows can be improved using gastroretentive systems.
2. For medications that are better absorbed in the stomach, such systems are helpful such as albuterol.
3. Gastroretention maintains consistent therapeutic levels for an extended period and reduces therapeutic level volatility, lowering the possibility of resistance, particularly in the case of antibiotics. e.g. antibiotics such as beta lactum (penicillins).
4. The bioavailability of drug delivery systems intended for once-daily administration, such as insulin, increases when drug delivery systems are retained in the stomach example-Ofloxacin.[16]

Factors controlling gastric retention of dosage forms

The structure and physiology of the stomach contain variables that should be taken into account when creating gastroretentive dose forms. Particles should be between 1 and 2 mm in size to pass through the pyloric valve and enter the small intestine.[17] Density, size, and shape of the dosage form, food intake and type, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity, and diseased states of the individual (such as chronic disease, diabetes, etc.) are among the most crucial factors affecting the gastric retention time (GRT) of oral dosage forms.[18] Other crucial factors include the drug's ionisation state, molecular weight, and lipophilicity.[19]

FORMULATION FACTORS

Density of dosage forms

The density of a dose form also influences the rate of gastric emptying and establishes where the system is located in the stomach. While high-density systems sink to the stomach's bottom, dosage forms with a density lower than the contents of the stomach can float to the surface.[20] Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.[21]

Shape and size of the dosage form

Designing indigestible single-unit solid dosage forms requires consideration of the shape and size of the dosage forms. Nonfloating dosage forms can be big, medium, or small units, and their size has a significant impact on their mean stomach residence durations.[22] The gastric retention time (GRT) is often inversely correlated with the size of the dose form since larger dosage forms make it more difficult for them to move swiftly via the pyloric antrum and into the intestine.[23-27] When compared to dosage forms with a 9.9 mm diameter, those with a diameter of more than 7.5 mm exhibit a longer stomach residence period.[28-32] Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.[32-36]

Viscosity grade of polymer

The viscosity of polymers and their interactions have a significant impact on drug release and floating properties of FDDS. High-viscosity polymers, like HPMC K4M, were found to be less effective at improving floating qualities than low-viscosity polymers, like HPMC K100 LV. Additionally, a drop-in release rate was seen as polymer viscosity increased.[37]

Idiosyncratic factors

Gender

Compared to men, women have slower stomach emptying times. Regardless of their weight, height, or body surface, the mean ambulatory GRT during meals (3.4–0.4 hours) is shorter than that of their age– and race–matched female counterparts (4.6–1.2 hours).[38]

Age

Older participants exhibit lower stomach emptying times than younger subjects. Gastric and intestinal transit times exhibit both intra- and inter-subject variability. Over 70-year-olds in particular have a much longer GRT than younger persons.[39]

Food intake and its nature

The amount of food consumed, its viscosity and volume, its caloric content, and the frequency of eating all have a significant impact on the retention of dosage forms in the stomach. The gastric retention time (GRT) of the dosage form is influenced by the presence or absence of food in the gastrointestinal tract (GIT). The gastric retention time (GRT) of the dosage form is often improved by the presence of food in the gastrointestinal tract (GIT), and as a result, the medication absorption increases by allowing it to remain at the absorption site

for a longer amount of time. Once more, a rise in acidity and caloric value results in a decrease in gastric emptying time (GET), which can enhance the retention of dose forms in the stomach.[25,26]

Table 1: Commonly used drug in the formulation of gastro-retentive dosages forms.[28,29]

Sr.No.	Dosage forms	Drugs
1.	Floating Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin
2.	Floating Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
3.	Powders	Several basic drugs
4.	Floating Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbide mononitrate, p-Aminobenzoic acid (PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil
5.	Floating Granules	Diclofenac sodium, Indomethacin, Prednisolone

Table 2: Gastroretentive products available in the market.[27]

Brand Name	Active Ingredient(s)
Topalkan®	Aluminum-magnesium antacid
Cytotec®	Misoprostol
Prolopa®	L-DOPA and Benserazide
Liquid Gavison®	Aluminum hydroxide, magnesium carbonate
Conviron®	Conviron Ferrous sulfate
Madopar®	L-DOPA and Benserazide
Almagate FlatCoat®	Aluminum-magnesium antacid
Valrelease®	Diazepam
Madopar®	L-DOPA and Benserazide
Cifran OD®	Ciprofloxacin
Oflin OD®	Ofloxacin

Potential drug candidates for gastroretentive drug delivery systems

1. Drugs that have narrow absorption windows in GIT

e.g. L-DOPA, p-aminobenzoic acid, furosemide, riboflavin.[30,35]

2. Drugs that are unstable in the intestinal or colonic environment

e.g. captopril, ranitidine HCl, metronidazole.[31]

3. Drugs that are locally active in the stomach

e.g.misroprostol, antacids.[32]

4. Drugs that disturb normal colonic microbes

e.g.antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin, and amoxicillin.[33,36]

5. Drugs that exhibit low solubility at high pH values

e.g. diazepam, chlordiazepoxide, verapamil[34]

Approaches to achieve gastric retention

High-density (sinking) system or non-floating drug delivery system

This method necessitates the development of dose forms whose density must be greater than that of the normal contents of the stomach (1.004 gm/cm3). The preparation of these formulations involves coating the medicine on a substantial core or combining it with inert substances such as iron powder, barium sulfate, zinc oxide, titanium oxide, etc.[40] The materials increase the density by 1.5–2.4 gm/cm3. For the stomach residence period to be significantly prolonged, a density of about 2.5 gm/cm3 seems necessary.[41] However, no evidence of this system's usefulness in humans has been found, and no system has been commercialized.[42]

Floating drug delivery systems (FDDS)

One of the crucial methods to induce gastrointestinal retention and produce acceptable drug bioavailability is to use floating drug delivery systems.[43] For medications with an absorption window in the stomach or upper small intestine, this administration strategy is preferred.[44] Due to their low density, these systems float over the contents of the gastrointestinal.[45] While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system as shown in fig. 1(a) To ensure that the buoyancy retention principle is properly achieved, a minimum degree of floating force (F) is also necessary to keep the dose form consistently buoyant on the surface of the meal. An innovative apparatus for calculating the resultant weight has been described in the literature to measure the floating force kinetics. The apparatus works by continually measuring the force, F, needed to keep the submerged object in place (as a function of time). If F is higher on the positive side, as seen in fig. 1, the item floats better.[46,47]

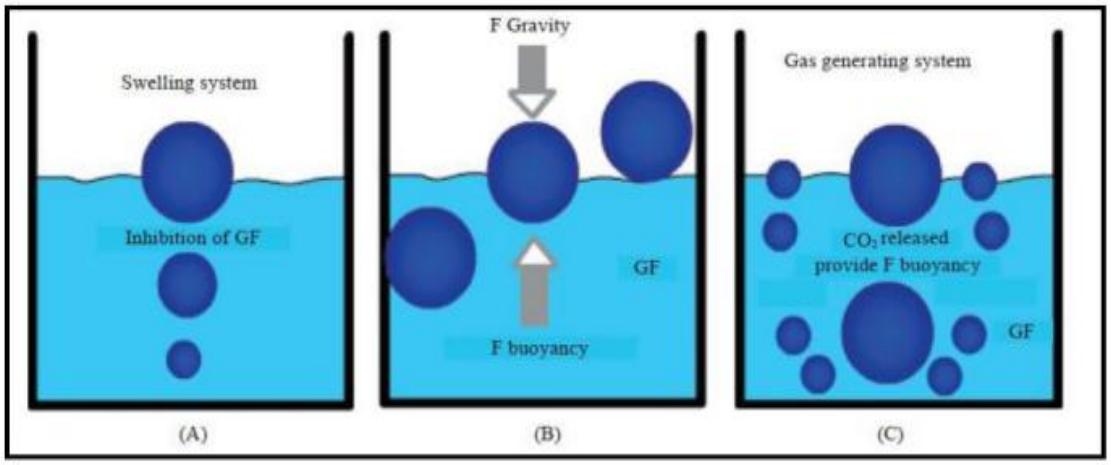
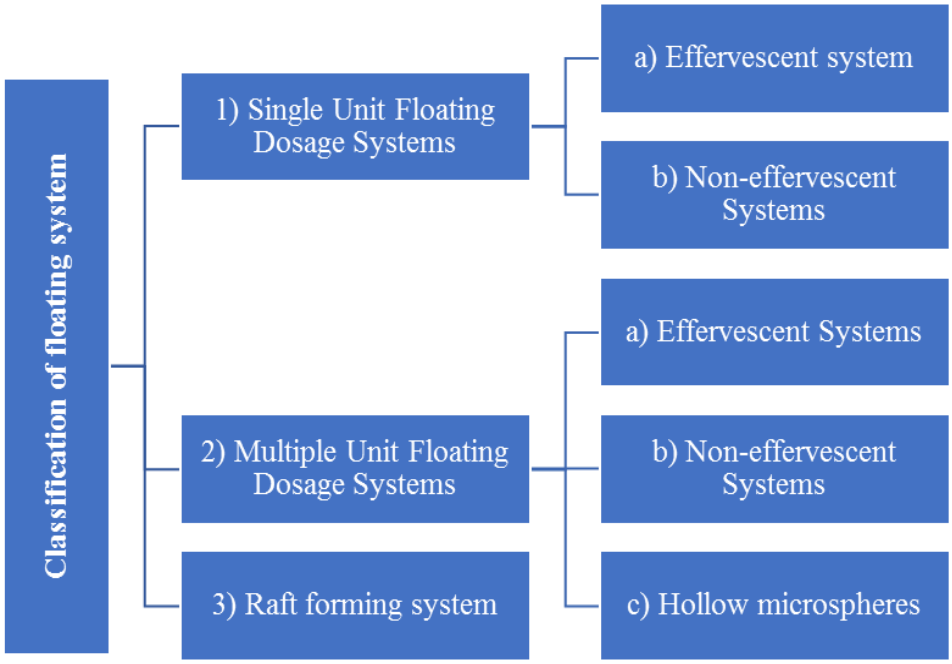


Fig 1: mechanism of floating of beads (GF=gastric fluid)

Classification of floating systems



1) Single Unit Floating Dosage Systems

The globular shells can be employed as a medication carrier for controlled release since they appear to have a lower density than stomach fluid.[48]

a) Effervescent system

Effervescent floating drug delivery systems produce gas (CO2), which lowers the system's density.[48] They float in the stomach for a long time and release the medicine gradually at a predetermined rate. These are matrix-type systems that have been developed with the help of swellable polymers like chitosan and sodium bicarbonate as well as several effervescent

substances like tartaric acid and citric acid. They are designed in such a way that when they come into touch with the acidic contents of the stomach, carbon dioxide (CO2) is released and gas is trapped in swelling hydrocolloids, giving the dosage forms buoyancy.[49] An expandable tablet made by Penners et al., which contains a mixture of polyvinyl lactams and polyacrylates, swells quickly in an aqueous environment and stays in the stomach for a long time. Additionally, gas-forming substances were also added, so that once the gas developed, the system's density decreased and it tended to float in the stomach environment.[50-52]

b) Non-effervescent Systems

Non-effervescent floating dosage forms use a gel-forming or swellable cellulose-type hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. For extended gastric residence, Iannuccelli et al. constructed an air compartment multiple-unit system. These units were made of a calcium alginate membrane and a calcium alginate core separated by an air compartment. It was discovered that the porous structure created by the polyvinyl alcohol (PVA) leaching, which was used as a water-soluble component in the coating composition, increased membrane permeability and prevented air compartment shrinking. As PVA and molecular weight grow, the capacity to float improves.[51]

2) Multiple Unit Floating Dosage Systems

a) Effervescent Systems

The goal of developing a multiple-unit dosage form may be to evenly distribute the medication content throughout the stomach, limit variability in absorption, and reduce the likelihood of dose dumping.[53]

b) Non-effervescent Systems

Compared to effervescent systems, there were fewer reports of non-effervescent multiple-unit systems in the literature. The feasibility of creating such a system including indomethacin using chitosan as the polymeric excipient, however, has only been mentioned by a few numbers of researchers. It is reported on a multiple-unit HBS that uses the model drug indomethacin and was created by the extrusion technique. Through the use of a needle, a mixture of the medication, chitosan, and acetic acid is extruded. By adjusting the drug-polymer ratio, it is possible to achieve the desired drug release since chitosan hydrates and floats in acidic solutions.[54]

c) Hollow microspheres

Floating microspheres have been manufactured using both natural and synthetic polymers. A floating dosage version of piroxicam based on hollow polycarbonate microspheres was developed by Joseph et al. By using a procedure called solvent evaporation, the microspheres were created. A95% encapsulation efficiency was attained. Male albino rabbits that were in good health underwent in vivo tests. The bioavailability of the piroxicam microspheres alone was 1.4 times that of the free drug and 4.8 times that of a dosage form consisting of microspheres plus the loading dose and was capable of sustained delivery of the drug over a prolonged period, according to pharmacokinetic analysis derived from a plasma concentration versus time plot.[55]

3) Raft forming system

As part of the raft production system, which includes the formation of viscous cohesive gel when in contact with gastric fluids, floating rafts have been employed in the treatment of gastroesophageal reflux disease (GERD).[56] A continuous layer known as a raft is formed as each liquid component swells. It has a low bulk density because the system's constituents contain a gel-forming substance, such as alkaline bicarbonates or carbonates, which causes the system to become less dense by producing CO2.[57] A gel-forming component of the system, such as sodium alginate, creates a foamy sodium alginate gel (raft) when it comes into contact with the stomach, preventing the reflux of stomach contents into the esophagus.[58]

CONCLUSION

Extending gastric retention of the dose form causes the time for medication absorption to be prolonged. Drug absorption in the gastrointestinal system is a highly varied process. Gastric retention might potentially be addressed with FDDS. There are several commercial products and patents issued in these sectors as proof. The goal is to increase the drug's bioavailability in the area of the gastrointestinal system with a limited window for absorption. Drugs that are less soluble at high pH are made more soluble by extending their time in the GI area, which also decreases drug waste and plasma level fluctuations. Despite the challenges that must be overcome to obtain longer stomach retention, several businesses are concentrating on commercialisation.

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