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Design and Development of Novel Floating Drug Delivery Systems

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Abstract

Recent advances in science and technology have greatly aided in the creation of novel drug delivery methods, especially in addressing physiological issues including irregular stomach emptying times and brief stomach residence periods. The purpose of gastro-retentive dosage forms (GRDF) is to stay in the stomach for a long time. Floating drug delivery systems, expanding or swelling systems, polymer-based bioadhesive systems, high-density systems, and other ways that postpone stomach emptying are just a few of the techniques that have been developed to do this. With an emphasis on the main floating mechanism utilized to accomplish stomach retention, this review attempts to gather contemporary literature. There are many advantages to sustained oral release of gastrointestinal dose forms, particularly for medications that act locally in the stomach and are absorbed in the upper regions of the gastrointestinal system. The review includes the physiology of the stomach, variables that affect the excipient's ability to retain food after it has been consumed, and methods for creating both multi-unit and single-unit hydrodynamically balanced systems. It goes into great length about these systems' classification, formulation, and evaluation in addition to discussing a few applications.

Keywords: Floating drug delivery systems, single unit, multiple units, evaluation in- vitro and in vivo, gastric residence time, Classification.

INTRODUCTION

Drug delivery systems are designed to transport pure, unaltered medications to specific areas of the body in various forms, such as solids, liquids, or semi-solids. For these systems to provide the appropriate dosage, reach the intended concentration, and sustain that concentration, they must be stable, safe, and therapeutically effective. A sizable share of medication delivery systems that are marketed are oral systems. Their easier administration, better patient compliance, and cheaper treatment costs make them the favored option. It may, however, need to be administered more frequently because the drug leaves the stomach quickly.

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Drug distribution methods need to offer a longer stomach residence time in order to get around these obstacles. Keeping the stomach full for an extended period improves the dissolution of drugs that struggle to dissolve in alkaline conditions. This approach also minimizes drug loss and ensures the medication is released at the right time for maximum effectiveness. Many drugs that are given in the stomach have optimal therapeutic benefits because of their controlled and delayed release. This distribution strategy does away with the necessity for regular dosing and decreases unwanted effects. Preparing drugs as bilayer or multilayered tablets is a unique technique to pharmacological dosing. This technique enables the loading dose and maintenance

dose to be administered together in a single tablet. A portion of the medication is released instantly into the first layer for rapid action, and it is released gradually into the second layer to maintain blood levels. Delivering the first dose, the immediate release part usually passes through the colon with its matrix layer intact, gradually dissolving to keep the blood level at the starting point.

When a medicine is taken orally, conventional controlled-release dosage forms frequently prolong the time it takes to take action. The drug from the sustained release layer then constantly releases the medication, giving layered tablets a pharmacokinetic advantage over single-layered tablets. This is because the drug from the rapid release layer increases plasma concentration quickly.

DEFINITION

Floating oral drug delivery systems (FDDS) are especially beneficial for medications that dissolve poorly or degrade in intestinal fluids. By staying in the stomach longer, they enhance the drug's stability and effectiveness. Their ability to float allows them to remain there for longer periods. This is due to their lower density compared to gastric fluids, which enables them to stay buoyant without affecting the stomach's natural emptying process. As a result, the medication remains suspended in the stomach contents and is released slowly at the right pace. The remaining system is finally drained from the stomach when the medicine has finished acting This allows the medication to stay in the stomach for an extended period, helping to maintain more stable drug levels in the bloodstream.

Medications Suitable for Gastro-Retentive Drug Delivery Systems

- Medications like misoprostol and antacids, which require extended contact with the stomach lining to be effective, benefit from prolonged retention in the stomach. Medications with a narrow absorption window in the digestive tract, like riboflavin and furosemide, which are best absorbed in specific sections of the gastrointestinal (GI) tract.
- Drugs that are unstable in the colon's environment, such as ranitidine HCl and captopril, which may lose effectiveness or degrade if they pass beyond the stomach too quickly.
- Medications that target harmful stomach bacteria, like those used to treat Helicobacter pylori infections, which require sustained presence in the stomach to work effectively.
- Drugs with low solubility in alkaline conditions, such as chlordiazepoxide and diazepam, which dissolve better in the stomach's acidic environment, ensuring optimal absorption.

Drugs Unsuitable for Gastroprotective Drug Delivery System:[8]

- Medications that barely dissolve in acidic conditions. e.g. Phenytoin, etc.
- Drug that, like erythromycin, is prone to breaking down in the stomach's acidic environment.
- Drugs like corticosteroids and 5-aminosalicylic acid that are mostly used with the purpose of releasing them specifically into the colon.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

a. Effervescent Floating Drug Delivery System
   1. Gas generating system.
   2. Volatile liquid containing system.

b. Non- Effervescent Floating Drug Delivery System
   1. Colloidal gel barrier system.
   2. Microporous compartment system.
   3. Floating microsphere.
   4. Alginate floating beads.
   5. Pec tin beads.
   6. Floating Minitablets
   7. Magnetic Systems.

c. Raft forming system

d. Unfordable, Swelling, Expanding and Superius Hydrogel System

Effervescent system floating drug delivery system:

These innovative drug delivery systems are made up of an expandable polymer like methylcellulose or chitosan, a specialized matrix, and effervescent components such as citric acid, tartaric acid, and sodium bicarbonate. These are made in a way that when they come into contact with stomach juice, they release CO2 while being encased in a hydrocolloid that swells to deliver the dosage type buoyancy. The design of the swellable asymmetric triple-layer tablet technique forms the core of the drug delivery system.[9]

Gas Generating Systems

Intra Gastric Single Layered Floating Tablets

The drug and carbon dioxide-generating agents are evenly blended within the matrix tablet to create a well-integrated formulation. These dose forms float in the stomach longer than gastric fluids because of their reduced density, which delays the emptying of the stomach. Any leftover medication is flushed out of the stomach once the entire dose has been released from the floating system. The control over plasma medication concentrations is improved by this prolonged stomach retention, leading to better therapeutic management.[10]

Tablets with a bilayer structure designed for intragastric use.

The two layers of these tablets are compressed as well.i.e.

1. Immediate release layer
2. Sustained release layer

Multiple Units Floating Tablets

The two outer layers of these systems encircle a core made up of sustained-release tablets. An expandable membrane makes up the outside layer, while effervescent agents are present in the interior layer. It quickly expands to create larger tablets that resemble balloons and float because of their decreased density when submerged in a body-temperature liquid. Because CO2 is produced and trapped within the systems, there is a lower density.[11]

Intra-gastric floating medication delivery devices with osmotic control and volatile liquid-containing components.

An air, vacuum, or other inert gas can be used in the flotation chamber of these devices to make them float in the stomach while holding a medicine reservoir.[12]

Inflatable Gastrointestinal Delivery Systems

With these systems, a liquid ether is placed inside an expanding chamber that vaporizes when it reaches body temperature, causing the chamber to expand inside the stomach. To create these systems, a polymeric matrix impregnated with a medication is placed inside an inflated chamber, which is subsequently enclosed in a gelatin capsule. Once the capsule dissolves after being taken orally, it releases both the drug reservoir and the expanded chamber. The inflatable chamber automatically retains the medication reservoir and inflates it into the stomach fluid.[13]

Intragastric Osmotically Controlled Drug Delivery Systems

It consists of a biodegradable capsule, an osmotic pressure-regulated drug delivery system, and a buoyant floating support. The capsule swiftly breaks down in the stomach to release the controlled intragastric osmotic medication delivery system. The inflatable support's inside creates a hollow, flexible polymeric bag that is inflated by a liquid that gasifier at body temperature. An osmotic pressure-controlled drug delivery system is made up of two main parts: the drug reservoir and the osmotically active compartment.[14] A pressure-responsive collapsible bag with a drug delivery hole that is impermeable to liquid and vapers encloses the drug reservoir compartment. Enclosed within the osmotically active compartment is a semipermeable housing that holds an osmotically active

salt.[15]Water from the gastrointestinal (GI) fluids is continuously drawn through the semi-permeable membrane into the osmotically active compartment, helping to dissolve the osmotic salt in the stomach. The collapsible bag is subsequently subjected to an osmotic pressure, which causes the reservoir compartment to condense and initiate the release of a medication formulation through the delivery aperture.[16]

Drugs delivery system floating and not dependent on effervescence.

Polysaccharides and matrix-forming polymers, such as polystyrene, polycarbonate, and polymethacrylate, combine to make hydrocolloids, cellulose derivatives with the ability to swell or form gels. These hydrocolloids are employed in non-effiervescent floating drug delivery systems. The common method of formulation involves combining the drug with hydrocolloids to create a gel that, when administered orally and in contact with gastric fluid, swells while maintaining shape integrity and a barrier of bulk density. The trapped air within the expanded polymer allows the dosage form to remain buoyant.[17]

Colloidal Gel Barrier Systems (Hydrodynamic Balanced Systems)

With this technique, the amount of medicine entering the absorption site in the solution phase is increased while the stomach retention period is prolonged. It primarily contains hydrocolloid-based drugs that form a gel, allowing them to remain buoyant on stomach fluids. Polysaccharides, hydroxypropyl methylcellulose (HPMC), and matrix-forming polymers such polycarbophil, polystyrene, and polyacrylate are examples of hydrocolloid celluloses that are present in such devices in one or more dosage forms. A gel barrier that functions as a colloidal shield against the environment is formed by the hydrocolloid's hydration upon exposure to gastrointestinal fluids.[18]

Systems comprised of small, permeable compartments.

With this method, a drug reservoir is encapsulated and pores are added to the top and bottom walls of a microporous compartment. The drug reservoir compartment's outside wall is completely sealed to keep any undissolved medication from coming into direct touch with the stomach surface. This allows the delivery system to float above the gastric contents by creating a floating chamber within the stomach's trapped air.

The amount of gastric fluid that enters the aperture hinders the medicine and carrier from continuously delivering the dissolved substance into the intestine for absorption[19].

Floating Microspheres/Micro Balloons

The most efficient buoyant object is believed to be hollow microspheres, commonly known as micro balloons. It makes up the microsphere's center void space. The hollow microsphere is filled with a medication created using a new solvent diffusion approach for emulsion in its outer polymer ring.[20]

Alginate Beads/Floating Beads

Multi-unit floating dosage forms can be developed using spherical calcium alginate beads, approximately 2.5 mm in diameter. These beads are formed by combining a sodium alginate solution with an aqueous calcium chloride solution, which causes calcium alginate to precipitate. To create a porous structure, the beads are then separated and rapidly frozen using liquid nitrogen. This is followed by a 24-hour freeze-drying process at -40°C. This designed system can sustain its floating ability for over 12 hours, ensuring that the floating beads remain in position for an extended duration 5.5 hours.[21]

PVA-PVP Spray Dried Tablets

These tablets demonstrate immediate floating with nearly no lag time, 24-hour floating, and non-sinking behavior. The GIT does not experience swelling or erosion, hence the release is independent of the medium's osmolarity.[22]

Ion Exchange Resins Beads

It has been demonstrated that a coated ion exchange resin bead formulation with bicarbonates put on it possesses gastric retention capabilities. Bicarbonate was used to load the ion exchange resins, and a negatively charged medication was then bound to the resin. [23]

Micro Particles

This method is based on powdered low-density foam. This system's zero to minimal lag time before flotation begins makes it favourable. These floating microcapsules, which were created using the emulsion solvent evaporation method, include model drug, polymers, and powdered polypropylene foam.[24]

Pectin Beads

The emulsion gelation technique was employed to create oil-entrapped calcium pectinate (CaPG) gel beads, serving as a carrier for intragastric floating drug delivery. To form these gel beads, an oil phase was carefully blended with a water phase containing pectin. The resulting mixture was then gently stirred and extruded into a calcium chloride solution at room temperature. If enough oil was utilized, the calcium pectin-ate gel beads became oil-entrapped and floated. Scanning electron photomicrographs showed the beads to have countless tiny pores, with sizes ranging from 5 to 40 m. The floating behavior of oil-entrapped CaPG beads varied based on the type and concentration of oil used. As a vehicle for intragastric floating drug administration, the oil-entrapped CaPG beads were a suitable choice.[26] For intragastric floating drug delivery, wax-incorporated calcium pectin-ate emulsion gel beads of metronidazole46 were created. Beads of calcium pectin-ate made using a modified emulsion- gelatin process. Some of the wax concentrations that we looked at were stearyl alcohol, polyethylene glycol, glyceryl monostearate, white wax, carnauba wax, and spermaceti wax. The waxes were thoroughly mixed, heated to a high temperature, and then extruded into calcium chloride solutions containing a blend of metropolitan pectin and olive oil.[27] The effect of various types and concentrations of wax on the floating and drug release behaviour of calcium pectinate emulsion gel beads was examined. When enough oil was utilized, the drug- loaded gel beads were demonstrated to float over simulated stomach fluid.[28] Wax was added to the emulsion gel particles and affected the release of the drug. Unlike water-insoluble waxes like glyceryl monostearate, stearyl alcohol, carnauba wax, spermaceti wax, and white wax, which greatly slowed down drug release, the water-soluble wax polyethylene glycol enhanced the release of the drug. However, some waxes had only a minor effect on the drug release rate.However, the formulations' enhanced wax content greatly prolonged the drug release while the beads continued to float.[29]

Floating Minitablets

Levodopa floating minitablets (MT) made from melt granulation and compression. According to the experiment, MT diameter and composition had the most effects on the drug release, which lasted for more than 8 hours. The 3mm MT produced at modest compression forces between 50 and 100 N had the best floating qualities.[30] It was discovered that dissolution patterns depend more on Methocel® K15M's capacity for sustained release than they do on levodopa's pH-dependent solubility. Ten healthy volunteers who had recently eaten were given sustained floating minitablets of levodopa for scantigraphic and pharmacokinetic tests. Levo-Form 1 (matrix) and Levo-Form 2 (coated), two concepts for sustained-release floating minitablets, were assessed and contrasted with the commercial product Prolopa®. HBS 125[31] The three formulations were found to offer nearly identical mean stomach residence times, which was about 240 minutes. One possible explanation for the more noticeable "peak and valley" effect on the levodopa plasma concentration-time profile is the existence of intragastric disintegration in Prolopa® HBS 125 and Levo-Form 2. Levo-Form 1 treatment, on the other hand, resulted in a more uniform distribution of levodopa's plasma concentration-time profile. Levo-Form 1 also offered the lowest variability in AUC and C max values between men and women.[32] Lastly, when the identical doses of the extracerebral dopa decarboxylase inhibitors carbidopa and benserazide were administered, benserazide's mean AUC, Cmax, and Tmax values were lower than those of carbidopa53.

A brand-new sustained release dosage form was created, containing both immediate and sustained release minitablets inside of a capsule made of hydroxypropyl methyl cellulose (HPMC). As reported by Ishida et al. (2008), the IRMT formulation includes low-substituted hydroxypropyl cellulose as a disintegrant, along with PSE and other excipients. The tablets were coated with HPMC, a water-soluble polymer. Low substituted hydroxypropyl cellulose content did not significantly affect PSE release in the IRMT generated with various amounts of this material because it all dissolved in the first 60Low substituted hydroxypropyl cellulose content did not significantly affect PSE release in the IRMT generated with various amounts of this material because it all dissolved in the first 60 minutes.[33]The SRMT contained only PSE and excipients and was coated with a blend of HPMC, a water-soluble polymer, and ethyl cellulose, a water-insoluble polymer. Variations in coat thickness and ethyl cellulose content in the polymer coat could be used to alter the lag period and PSE release profile for the SRMT, respectively. PSE in the SRMT was released over the course of 8–10 hours, but PSE in the IRMT crumbled after 60 minutes. PSE was rapidly released from the contained tiny tablet system and was sustained over a lengthy period of time. Furosemide 54 floating minitablets were created using the gas formation process.[34] A solid dispersion of povidone, furosemide, and various excipients is one of the system's main parts. A sodium bicarbonate-containing effervescent layer and an outer polymeric layer composed of polymethacrylates are applied in succession to these core units. In order to float within a reasonable time frame, only systems containing Eudragit RL30D or a combination of these polymers in the outer layer were successful. As effervescent agent concentration rose and polymeric layer coating level dropped, the time it took for the system to float reduced. By varying the polymeric layer's coating level, the drug release rate could be regulated and was linear with respect to the square of time. The polymeric layer's coating level was increased, which slowed the drug release rate. Both controlled release qualities and fast floating were attained in this investigation. The units were found to have been in the stomach for roughly six hours, as determined by radiogram analysis of the in vivo gastric residence period.[36]

Magnetic systems

This technique is based on the idea of placing a small internal magnet within the dosage form while using a larger external magnet over the abdomen, aligned with the stomach's location. Although several experiments have shown promising results, the practical effectiveness of this approach remains uncertain, as it relies on precisely positioning the magnet to achieve the desired effect. Future advancements in more user-friendly magnetic field sources may help refine and enhance this concept.[37]

Raft-Forming Systems

Antacid and medication delivery for gastrointestinal infections and illnesses via raft-forming devices are receiving a lot of attention. A gel-forming solution swells in reaction to stomach juice, creating a cohesive, viscous gel that gets caught in carbon dioxide bubbles. The raft-like layer that forms on the gastric fluid's surface enables the drug to be released slowly into the stomach.[38]

Unfordable, Swelling, Expanding and Superius Hydrogen Systems

The dose form in this sort of expandable system will endure gastric transit, but it must be tiny enough to be eaten and must not obstruct the stomach when taken alone or in combination with other medications.[39] Biodegradable polymers are used to create unfordable systems.[40] After being swallowed, dose forms with swelling and expanding systems swell to some amount before emerging from the pylorus. This kind of dose form is retained for a long time in the stomach. Under this method, swelling and controlled drug release can be achieved, just like when the drug comes into contact with stomach fluid. New developments in the field have led to the creation of super porous hydrogel hybrids, which have an average pore size of more than 100 micrometers. These hybrids are created by adding a hydrophilic or water dispersible polymer after the super porous hydrogel has developed. Among the polysaccharides that are considered hybrid agents include sodium alginate, chitosan, and pectin.[41]

Factors Affecting Floating Drug Delivery System

1. *Density:* Buoyancy of dose forms, which depends on density, is a factor in floating.
2. *Shape of dosage form:* Tetrahedron and ring-shaped devices are highly buoyant, maintaining 90% to 100% floatation even after 24 hours. With flexural moduli of 48 and 22.5 kilopounds per square inch (KSI), they outperform other shapes in efficiency.[42]
3. *Concomitant drug administration:* Opioids such as codeine, prokinetics such as metoclopramide and cisapride, and anticholinergics such as atropine and propantheline can all affect the floating time.
4. *Fed or unfed state:* Gastrointestinal (GI) motility during fasting is distinct due to the migrating myoelectric complex (MMC), which occurs at regular intervals1.5 to 2 hours, or bursts of high motor activity.[43]
5. *Nature of meal:* When indigestible polymers or fatty acid salts enter the stomach, they trigger a shift in its motility pattern, mimicking a fed state. This can hold down the emptying of the stomach and postpone the release of medications.[44]
6. *Caloric content and feeding frequency:* A protein- and lipid-rich meal can prolong flotation for an additional four to ten hours. Multiple meals instead of only one can cause the floating to stretch by more than 400 minutes because of the low frequency of MMC.
7. *Age:* The lifespan of the elderly is much longer—especially for those over 70. Diseases including diabetes, Crohn's disease, and others have an impact on how drugs are delivered.
8. *Posture:* The patient could be floating in a supine or upright position.[45]

Table 1. Comparison Between Conventional and Floating Drug Delivery Systems:[46]

Conventional Drug Delivery System	**Floating Drug Delivery System**
More side effect.	No risk of dose dumping.
Patient compliance is less.	Improves patient compliance.
Less gastric retention time.	Improves gastric retention time.
Not suitable for delivering drugs that have a limited absorption window in the small intestine.	Ideal for delivering drugs that have a restricted absorption window in the small intestine.
Not suitable for drugs that act locally in the stomach, break down in the colon, and are rapidly absorbed through the gastrointestinal tract.	Ideal for drugs that work locally in the stomach, break down in the colon, and are quickly absorbed through the gastrointestinal tract.

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

The stomach is divided into three main sections: the fundus, the body, and the antrum (pylorus). Primarily in charge of mixing motions, the antrum propels movements that help empty the stomach by acting as a pump. Undigested food is stored in the fundus and body of the stomach, which make up the proximal portion of the stomach. While the patterns of motility vary between the fed and fasted stages, gastric emptying happens in both. While fasting, the stomach and intestines undergo an electrical event every two to three hours. This cycle, called the four-stage migrating myoelectric complex (MMC) or interdigestive myoelectric cycle, plays a key role in controlling digestive activity.

a. Phase I: Because MMC is delayed at this point, the stomach emptying rate is slow. This stage often lasts for thirty to sixty minutes. There is no contraction during this process. It is also referred to as the basal phase.
b. Phase II: In this stage, bile secretion, mucus discharge, and intermediate contraction occur. Between 20 and 40 minutes are spent on it. Occasionally, the pre-burst process is used to describe it. Both the intensity and frequency increase steadily as the process goes on.
c. Phase III: During this phase, there is a brief period of frequent, intense contraction. Typically, it goes for 10 to 20 minutes. This process is frequently referred to as a "housekeeper wave" since it seems to drain the stomach's fasting contents. During this phase, large targets are moved to the small intestine but stay in the stomach to be fed.
d. Phase IV: This step, which comes after phases III and I, lasts between 0 and 5 minutes. Following ingestion of a mixed meal, the contraction pattern shifts from the fed state to the fasted state. Constant contractions are involved, just as they are in step II's fasting situation, and this is

frequently referred to as the pattern of digestive motility. These contractions break down food particles, reducing their size to less than 1 mm as they move in suspension toward the pylorus. Due to the delayed initiation of MMC during the fed state, the rate of stomach emptying is reduced.[47] (Fig2)

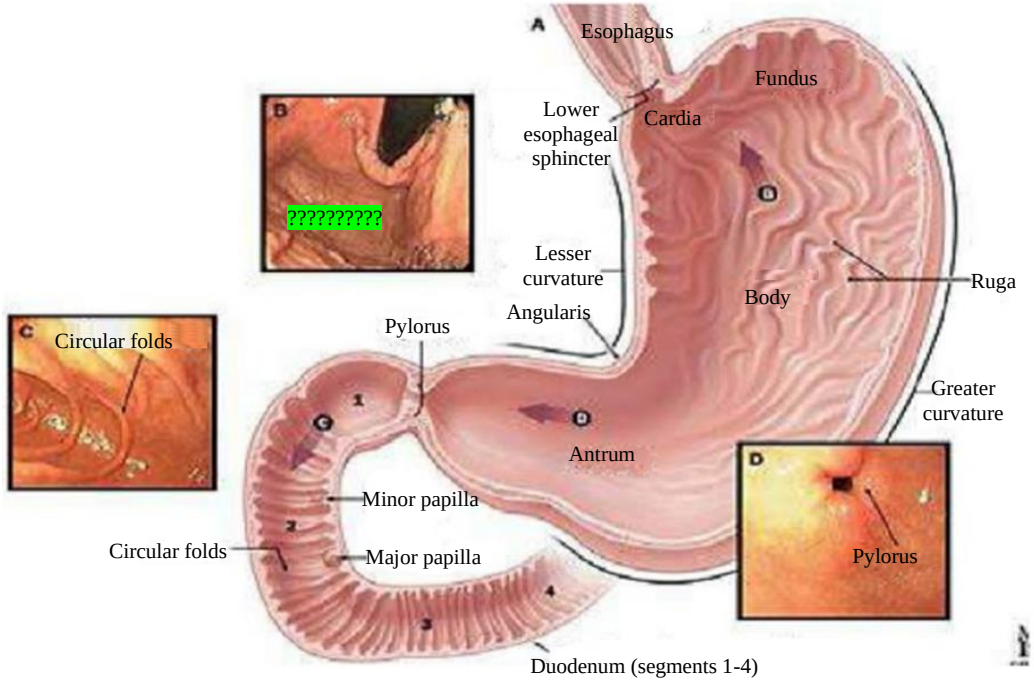

Figure 1. Physiology of stomach.

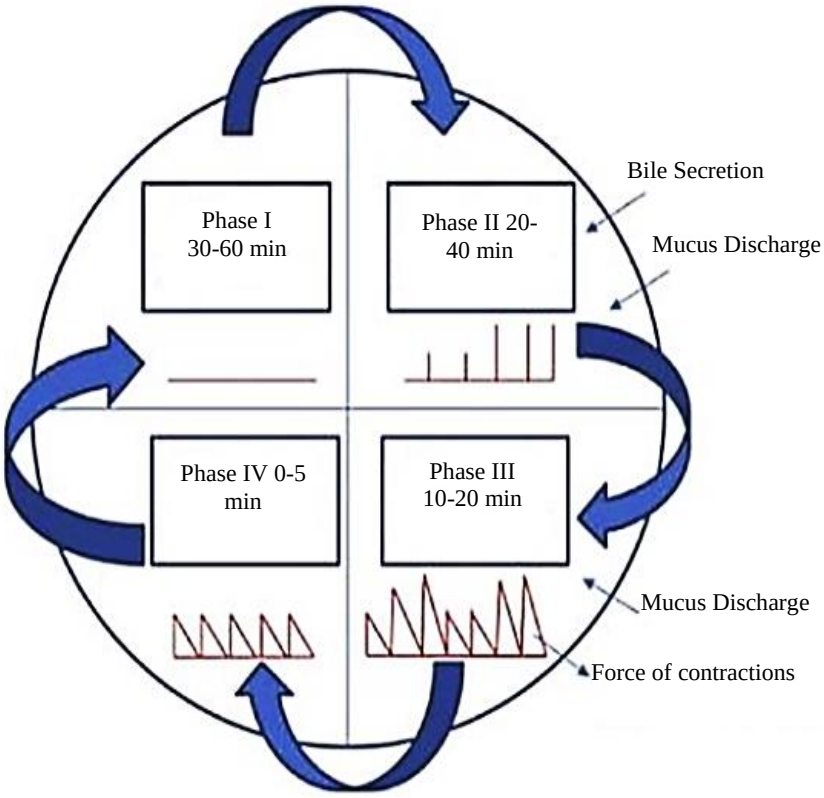

Figure 2. Motility Pattern in GIT.

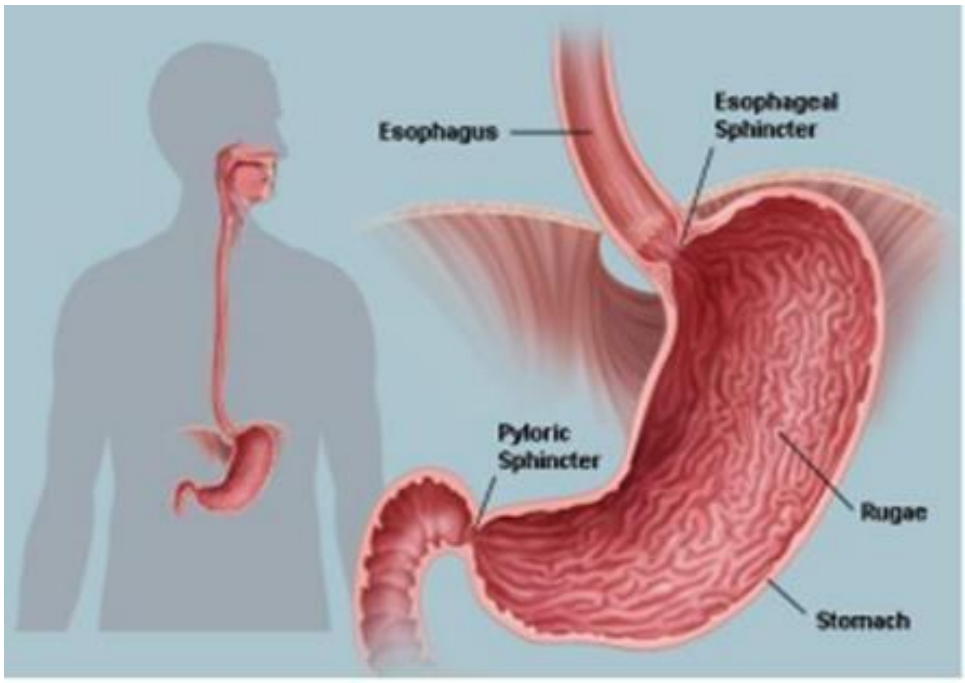

Figure 3. Gastro intestinal tract.

MECHANISM OF FLOATING SYSTEMS

Different approaches have been studied to extend the time dosage forms remain in the stomach. These include floating dosage systems (gas-generating and swelling or expanding formulations), mucoadhesive systems, high-density systems, modified-release forms, gastric-emptying delay devices, and the simultaneous use of medications that slow gastric emptying. Among these, floating dosage systems are the most commonly utilized. Floating drug delivery systems (FDDS) are designed with a lower density than gastric fluids, allowing them to remain in the stomach for an extended time without interfering with the natural gastric emptying process. Even while floating on gastric contents, these systems gradually release the medication at a controlled rate. Once the drug is fully released, the remaining system is eventually removed from the stomach.[49] The outcome is improved GRT and more control over variations in medication concentration in plasma. As minimum stomach content is required to enable correct fulfillment of the buoyancy retention principle, so too is a minimum level of floating force (F) required to keep the dose form continually buoyant on the meal's surface. A specialized instrument continuously measures the force corresponding to F (as a function of time) to stabilize the submerged object and analyze the dynamics of the floating force.fiftyF on the higher positive side will result in a better floating item.

$$F = F_{buoyancy} - F_{gravity} = (Df - Ds)\, v.g$$

Where, F= total vertical force; Df = fluid density; Ds = object density; v = volume , g = acceleration due to gravity.[51]

Approaches to Design Floating Drug Delivery System

For Single Unit Dosage Forms (Ex: Tablets)

a. *Floating Lag Time:* This is the duration, measured in seconds or minutes, that a tablet requires to ascend and remain afloat on the surface of the dissolution medium.
b. *In-vitro drug release and floating duration:* This process involves agitating synthetic gastric juice (pH 1.2, without pepsin) at 37.2°C using USP II paddle devices set at either 50 or 100 rpm. Samples are taken at regular intervals, and their drug content is then analyzed. The floating duration, measured in hours, is visually assessed by observing how long the tablet remains afloat on the dissolution medium.

c. *In-Vivo Gastro-Retention Assessment:* This involves tracking the movement of the dosage form in the gastrointestinal tract using X-ray imaging or gamma scintigraphy. Additionally, the tablets are tested for characteristics such as hardness and weight variation.

Hydrodynamically Balanced System

This administration method is designed to improve drug absorption and extend the residence time of certain medications in the gastrointestinal tract. Drugs formulated using the HBS system exhibit higher solubility in acidic environments and are primarily absorbed in the upper small intestine. For extended retention in the stomach, the dosage form must steadily release the drug while keeping its bulk density below 1.

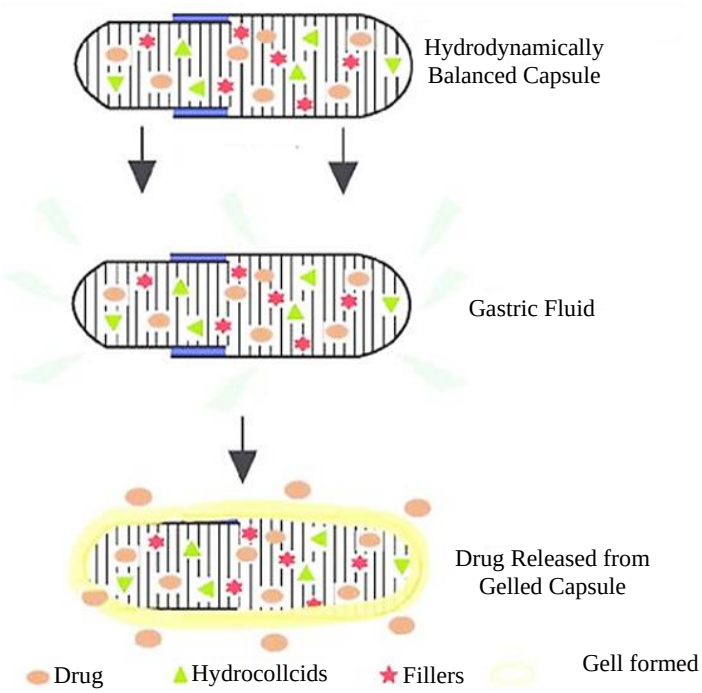

Figure 4: Working principle of Hydrodynamically Balanced System. For Multiple Unit Dosage Forms (Ex: Microspheres):

Scanning Electron Microscopy (SEM) is used to examine the surface structure and dimensions of a sample in detail. Additionally, an optical microscope can be used to measure its dimensions accurately.

In-vitro Floating Potential (Buoyancy Level)

To evaluate buoyancy, a measured quantity of microspheres is dispersed in 900 mL of 0.1 N HCl containing 0.002 v/v Tween 80 and agitated at 100 rpm using a USP Type II dissolution system for 12 hours. Afterward, the floating and settled fractions are separated, dried in a desiccator, and weighed. Buoyancy is then determined using a specific formula. Buoyancy (%) = W_f (W_f +W_s) X 100
where (W_f) and (W_s)are the weights of the floating and settled microspheres, respectively.

Fourier Transform Infrared Spectroscopy (FTIR) is a widely used technique for analyzing interactions between drugs and excipients. The presence of a new peak or the disappearance of an existing peak in the spectrum indicates a potential interaction between the drug and the excipient.

Techniques for Formulating Floating Drug Delivery Systems

- *Direct Compression Technique:* This process involves directly compressing tablets from powdered ingredients without altering their physical properties. Common carriers used in this method include tricalcium phosphate and dicalcium trihydrate phosphate.

- *Effervescent Technique:* The floating chamber of the drug delivery system is filled with inert gas (CO_2), which is generated through an effervescent reaction between bicarbonate salts and an organic acid, such as citric acid.
- *Wet Granulation Technique:* This method involves crushing, drying, or blending moist powder. Instead of compressing powders directly, wet granulation forms granules by using a binding agent to hold the particles together.
- *Ionotropic Gelation Technique:* Using oppositely charged calcium ions, the natural polymer anionic polysaccharide sodium alginate gels to produce instantaneous microparticles.
- *Solvent Evaporation Method:* This technique takes use of the continuous phase's limited ability to extract the liquid dispersion solvent in its whole. Microspheres become toughened as a result of the solvent evaporating from the dispersion surface.
- *Spray Drying Technique:* This method involves blending the core layer with a liquid coating solution and then spraying the mixture into the air. As the liquid evaporates quickly, the coating material hardens and forms a solid layer around the core.
- *Melt Solidification Technique:* In this method, the molten material is dispersed into an aqueous phase as an emulsion and then cooled to facilitate solidification. Common carriers used for this method include lipids, waxes, and polyethylene glycol.
- *Melt Granulation Technique:* This technique binds medicinal powders together using a meltable binder, without the need for organic solvents or water.

Excipients Used in Various Floating Dosage Forms:[56]

- *Effervescent Agents:* Some examples include disodium glycine carbonate (Di-SGC), sodium bicarbonate, citric acid, tartaric acid, and citroglycine (CG).
- *Release rate Retardants:* Various ingredients, including talc, magnesium stearate, and dicalcium phosphate, are used to slow down the drug release rate.
- *Inert Fatty Materials:* Examples include beeswax, fatty acids, long-chain fatty alcohols, and Gelucires 39/01 and 43/01.Release rate enhancers: For example, lactose, mannitol.
- *Hydrocolloids:* Examples include Acacia, β-cyclodextrin, Pectin, Alginates, Gelatin, HPMC, and carbopol.
- *Buoyancy increasing Agents:* Such as Acurel MP 1000, a powder made of ethylene and polypropylene.

Application of Floating Drug Delivery System

Enhanced bio-availability

Riboflavin CR-GRDF shows a much higher bioavailability than conventional non-GRDF CR polymer-based formulations. The degree of drug absorption is influenced by several gastrointestinal processes related to drug uptake and transit.[57]

Enhanced first-pass bio transformation

Comparable to the increased effectiveness of capacity-restricted active transporters, submitting the drug to the metabolic enzymes (cytochromium P450, specifically CYP3A4) over an extended period of time instead of injecting it all at once can significantly boost the pre-systemic metabolism of the compound under test.[58]

Sustained delivery of drugs/reduced dosing frequency

Sustained and slow feedback from CR-GRDF can result in flip-flop pharmacokinetics for drugs with a relatively short biological half-life and allow for decreased dosing frequency. This function is related to enhanced patient compliance, thereby enhancing therapy.[59]

Targeted therapy for local ailments in the upper GIT:

GRDF-based medications provide steady and extended drug release, making them ideal for targeted treatment in the stomach and small intestine. Through this form of administration, therapeutic

medication concentrations may be attained locally, whereas little systemic drug concentrations remain after drug absorption and distribution. [60]

Reduced medication concentration variations

Continuous infusion of the medication after CR-GRDF injection results in blood drug concentrations within a tighter range compared to instant release dose forms. As a result, drug impact variations are diminished and peak dose-related side effects that are concentration- dependent can be avoided. This function is particularly crucial for pharmaceuticals with a limited therapeutic index.[61]

Minimization of fluctuations in drug concentration

Drugs that activate distinct types of receptors at different concentrations can have a pharmacological response that is somewhat selective.[62]

Reduced body counter-activity

In some instances, the body can bounce back and lessen the effects of the medicine due to the pharmacological reaction that disrupts regular physiological functions. Slow drug absorption into the body was observed to lower counteraction and increase drug efficacy.[63]

Extended time over critical concentration (effective)

For some medicines, such beta-lactam antibiotics, whose pharmacodynamics are not concentration-dependent, the duration over critical therapeutic concentrations is more important in determining the clinical response than peak concentrations. The continuous administration strategy enhances the pharmacological effects and improves therapeutic outcomes by prolonging the duration above a threshold concentration.[64]

Minimized adverse activity at the colon

Gastro-retentive Dosage Forms (GRDF) help limit the amount of medication reaching the colon by keeping the drug in the stomach, potentially reducing any adverse effects in that area. Since that the small intestine is the only organ from which beta-lactam antibiotics are absorbed, this formulation idea is especially important. The pharmacodynamic reasoning behind GRDF formulations for these antibiotics is highlighted by the possibility that their presence in the colon may lead to a rise in microbial resistance.[65]

Site specific delivery of drugs

A floating dosage system is an effective solution, particularly for drugs that are primarily absorbed in the upper small intestine. The drug's systemic exposure is decreased and enough local therapeutic levels are provided via the medication's regulated, slow distribution to the stomach. This lessens adverse drug-related effects on the blood supply. The frequency of dosage can also be reduced by extended gastric availability from a delivery method directed at the location.[66]

Pk And Pharmacodynamic Aspects Of Grdf:

In order to determine which input method would be most advantageous for generating significant therapeutic gains, it has been shown that the correct drug delivery system selection should conform with the PK and pharmacodynamic features of the drug. To establish the logical choice of GRDF as the optimum route of administration for some medications, it appears to be crucial to define a variety of PK and pharmacodynamic factors.[67]

Active transport mechanism

A persistent presentation of the medication to the transporting enzymes may increase the efficacy of the transport and hence improve bio-availability when absorption is mediated by active transporters with capacity limits.[68]

Elimination half-life

A flip-flop PK is seen when medicines with a very short biological half-life are introduced into a CRGRDF. This may make it possible to provide doses less often, which would enhance patient compliance and therapeutic results.[69]

Pharmacodynamic Aspects of GRDF:

For the majority of medications, a better delivery method would dramatically lessen blood level fluctuations, improve the medication's therapeutic effectiveness, and lessen its concentration-dependent side effects. For medications like L-Dopa that have a very narrow therapeutic index and absorption window, this aspect is especially crucial. There are several pharmacodynamic factors that need to be taken into account, even if the continuous and prolonged mode of administration attained by CR-DFs is mostly related to the PK benefits.[70]

Selectivity of receptor activation

Receptor selectivity: Receptor types that are activated by medicines at different concentrations can be best regulated by minimizing fluctuations and achieving higher drug plasma levels. Low rebound activity (64). A given substance is more likely to cause a rebound effect when it interferes with normal physiological functions. This can be successfully prevented by the medicine's gradual absorption into the bloodstream, which will reduce counter-activity and boost drug effectiveness.[71]

Enhancing beta-lactam activity

The clinical response of some medications, such as beta-lactam antibiotics, is not correlated with peak concentration but rather with the amount of time spent above a key therapeutic concentration. These medications exhibit non concentration-dependent pharmacodynamics. These medications' efficacy could be improved by using SR formulations, which could prolong the duration that plasma levels remain above the threshold.[72]

Evaluation of Floating Drug Delivery System

In Vitro Evaluation

1. *Density:* The following formula was used to calculate the bulk density and tap density: Powder weight divided by powder volume in the measuring cylinder equals bulk density. Powder weight / Tapped capacity in measuring cylinder equals tap density.
2. *Procedure:* A 10 ml measuring cylinder was filled with 2 grams of powder. The first step in determining bulk density is to record the original volume. Tapping is then maintained until no additional changes in volume are noticed.[73]
3. *Angle of Repose:* The fixed funnel method was used to determine the angle of repose. The funnel was unscrewed to allow the finely measured powder to flow through. On a stand, the funnel is adjusted to a precise height. The cone heap's height and the powder's radius were recorded. Next, the angle of repose was computed using the given formula. $\tan \theta = h / r$ $\theta = \tan^{-1} (h/r)$, Since θ is the angle of repose h = the heap's height, radius of the heap = r.[74]
4. *Carr's Compressibility Index:* By comparing the powder's bulk density and tapped density, one can ascertain the material's flow ability. The formula for calculating Carr's index was: Carr's index = (tap density – bulk density) ×100 / tap density.[75]
5. *Hausner Ratio:* The Hausner ratio of every pill blend was also determined using the formula that follows: Calculus: tapping density / bulk density.[76]
6. *Moisture Content:* Moisture content is determined by means of Karl Fisher titration.[77]
7. *Shape of The Tablets:* Under the magnifying lens, compressed tablets intended for FDDS are examined to determine the quality of their shape.[78]
8. *Tablet Dimension:* The thickness and diameter of tablets in FDDS shape are determined using a calibrated Vernier calliper, the same as that of traditional tablets, as per the official compendium. Three tablets are randomly chosen from each formulation, and their thickness is measured individually.[79]

9. *The Tablet's Hardness:* A total of twenty tablets, randomly selected from each batch of formulations, should be tested for hardness using a Monsanto-style hardness tester.[80]
10. *Friability Test:* The Friability instrument was utilized to assess the friability of tablets. The percentage (%) is used to express it.[81]

Variation of Weigh

Twenty tablets chosen at random are correctly measured and the tablet's average weight is determined. And the individual weight difference is determined from the average weight.[82]

Floating Power Assessment

Three separate tablets are put into an individual flask that has 400 ml of 0.1(N) HCL solutions in it. Subsequently, the duration in minutes required for every tablet to ascend to the top of the flask (known as the floating lag time) and remain continuously afloat on the water's surface (known as the floating duration) are ascertained. Next, the mean and standard deviation of the sample are computed.[83]

The Formulation Density

The tablets' apparent densities are measured in triplicate from their volumes and masses. Using the cylinder mathematical equation and the measured height (h) and radius (r) of the cylindrical tablets (r) using a micrometer gauge, the volume V of the tablets is calculated. (V

= A x r2 x h).[84]

Contents of Medications in Tablets

A 100 ml volumetric flask filled with 0.1(N) HCL is randomly selected to include ten tablets from each batch. After storing for two hours, withdraw 1 milliliter from the volumetric flask and transfer it to a test tube. Samples are screened, then suitably diluted and spectrophotometrically analyzed at the proper wavelength.[85]

Analysis of In Vitro Dissolution

The tablet was placed inside the dissolution vessel, and 5 ml samples were collected at specific time intervals—1h, 2h, 3h, 4h, 5h, 6h, 8h, 10h, and 12h—or at other necessary intervals. To maintain a total dissolution fluid volume of 900 ml, 5 ml of fresh dissolution medium was added after each sample collection. The release experiments were conducted using "n" tablets, and the average values were plotted against time. Each sample was analyzed using a UV-visible spectrophotometer against a reagent blank at its maximum wavelength, and the corresponding concentration was determined from the calibration curve.[86]

Test of Buoyancy/Floating

It measures how long the dosage form stays buoyant and how long it takes for the buoyancy of the simulated stomach fluid to change once the dose form is introduced. Total floating time, also called buoyancy lag time (BLT) or floating lag time (FLT), refers to the duration a dosage form stays afloat after surfacing in a medium.[87]

Floating properties

A continuous floating monitoring system, along with a statistical experimental approach, was used to evaluate the impact of formulation variables on the floating behavior of the gastric drug delivery system.[88]

Percentage Yield (%)

One can calculate the percentage yield of floating micro-spheres by dividing the product's actual weight by the total number of non-volatile components. Following formula may be used to calculate % yield = weight of floating microscopes/weight of drug and polymers X $_{100}$.89

Drug Entrapment Efficiency

The effectiveness of drug trapping in microspheres can be measured by precisely weighing a certain quantity of microspheres and appropriately smashing them using a mortar and pestle.

The crushed material will then be suspended in the pre-measured amount of acid buffer and left for a full day. The content is then filtered, and the filtrate is examined using spectrophotometry at an appropriate wavelength. This formula will be used to determine the percentage of drugs entrapped: Formulating Entrapment Efficiency: Dose content / Theoretical Drug content x 100.[90]

Analysis of Swelling

The floating tablets (designated as W0) were weighed one at a time and then placed individually in a glass beaker with 200 ml of 0.1 N HCl. The beaker was then incubated at 37°C ± 1°C for 24 hours at regular intervals. After removing the floating tablets from the beaker, gently blot any excess liquid from the surface using tissue paper. The swollen tablets were then weighed again (Wt.), and the percentage swelling index (SI) was calculated using the following formula:

Swelling Index % (SI) = [(Wt – W0) / W0] × 100

Where, S.I. = Swelling index, Wt = Weight of tablet at time t , W0 = Weight of tablet before placing in the beaker.[91]

Surface Topography

Surface topography and structural analysis were conducted using atomic force microscopy (AFM), contact angle meters, scanning electron microscopes with a 10 kV acceleration voltage, and contact profilometers.[92]

Powder X-Ray Diffraction

Pharmaceutical solids are routinely characterized using X-ray powder diffraction, which is the primary method for studying polycrystalline materials.[103] Analysis of Infrared Fourier Transform The primary applications of Fourier transform infrared spectroscopy are in the identification of organic, polymeric, and certain inorganic materials, as well as the determination of functional groups.[93]

Differential Scanning Calorimeter (DSC)

Pharmaceutical hydration and water content are analyzed by DSC. Thermograms of prepared materials are measured using a DSC apparatus equipped with an intercooler. Zinc standards are used to calibrate both the DSC temperature and the enthral scale.[94]

Stability Studies

The ideal formulation was kept for stability tests in a chamber (therm lab) for three months at 40ºC±2ºC and 75±5% relative humidity. Changes in weight, physical appearance, in-vitro drug release, and drug content were observed at one-month intervals.[95]

In Vivo Evaluation

X- Ray Method

An extensively used measure for floating dosage form assessment is the X-ray method. Understanding the dose form's location in the gastrointestinal tract as well as how to forecast and correlate its timing for emptying the stomach are helpful. Because the radio-opaque material is present in a solid dosage form in this instance, it may be seen on an X-ray.[96]

Gamma Scintigraph

When formulated into dose forms with controlled release, gamma-emitting radioisotopes have become the most advanced method for determining the gastro-retentive formulation in individuals in good health. Gamma scintigraphy has several drawbacks, the main ones being the associated ionizing radiation for the patient, the lack of appropriate topographic data, and the expensive production of radiopharmaceuticals.[97]

Gastroscopy

A gastroscopy may be performed in order to examine the effects of GRDDS's prolonged stay in the stomach environs. It is also possible to extract GRDDS from the stomach for a more comprehensive evaluation of the formulations.[98]

Ultrasonography

Ultrasonic waves reflect dramatically different acoustic impedance across interfaces, allowing for the visualization of several abdominal organs (55). Most FDDS do not display perceptible audio mismatches during interactions with the physiological environment. Therefore, ultrasonography is not widely used for evaluating FDDS. The characterization process evaluated the intragastric positioning of hydrogels, how solvents penetrated the gel, and the interactions between the gastric wall and FDDS during peristalsis.[99]

Magnetic Resonance Imaging

Recent studies in the field of gastrointestinal research have demonstrated the value of magnetic resonance imaging (MRI) for the investigation of stomach emptying, motility, and the intragastric distribution of macronutrients and pharmacological models. MRI's benefits include less ionizing radiation, excellent soft tissue contrast, and good temporal and spatial reolution.[100]

Pharmacokinetic Studies

An essential component of in vivo research is pharmacokinetic analysis, which has been the subject of numerous published papers. The pharmacokinetics of verapamil were investigated by Sawicki using floating pellets that were put into capsules and compared to traditional 40 mg verapamil tablets. Compared to the usual verapamil tablets, the floating pellets showed a greater t max and AUC (0infinity) value (3.75 h and 364.65ng /ml ..1h, respectively). (1.21 hours for the tmax value and 224.22 mg/ml for the AUC value).[101]

Drug Candidates Suitable For Floating Drug Delivery System:[102]

- Those medications (such as L-DOPA, p-aminobenzoic acid, furosemide, and riboflavin) with a limited window of absorption in the GIT.
- Medication that acts locally in the stomach (antacids, for example) [10] medications that become unstable in the colonic or intestinal environment (captivator, itinerant HCL, metropolitan, etc.).
- Substances that disrupt the usual bacteria in the colon (such as antibiotics like tetracycline, clarithromycin, and amoxicillin that are used to eradicate Helicobacter pylori).
- Medications with poor solubility at high pH levels include verapamil, chlordiazepoxide, and diazepam.

EXCIPIENTS USED IN Floating Drug Delivery System

Polymers

Polymers are long-chain organic compounds that are put together from several monomers, which are smaller molecules. It helps with the FDDS preparation that is directed toward the GIT. 103 Hydrophilic Polymers: Examples include egg albumin, gelatin, agar, starch, chitosan, and cellulose derivatives like HPMC and DEAE cellulose.[104]

- *Hydrophobic Polymers:* These include acrylic acid esters, polylactic acid, ethyl cellulose, and PMMA.
- *Biodegradable Polymers:* These materials gradually break down at the administration site through chemical processes like hydrolysis. Examples include polyglycolic acid (PGA), polycaprolactone (PCL), polylactic acid (PLA), as well as broader categories such as polyanhydrides and polyorthoesters.[105]
- *Soluble Polymers:* These are water-soluble, uncross-linked polymers with a moderate molecular weight (below 75,000 Daltons). As the molecular weight increases, the dissolution rate decreases. They can be used individually or in combination with hydrophobic polymers to create materials

that degrade gradually. Examples include copolymers of methacrylic acid and acrylic acid methyl ester (Eudragit L), hydroxypropyl methylcellulose (HPMC), uncross-linked polyvinyl alcohol, polyvinyl pyrrolidone, and polyethylene glycol (PEG).[106]

- *Inert Fatty Materials:* (5%–75%) It is possible to boost buoyancy by decreasing the hydrophilic property of a formulation by using edible, inert fatty material with a specific gravity less than one. For example, long chain fatty alcohols, fatty acids, beeswax, and Gelucires 39/01 and 43/01.[107]

Table 2. List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems[108]

Dosage Form	Drug
Tablets	Acetylsalicylic acid, nimodipine, Furosemide, Ciprofloxacin, Captopril, cholerpheniramine maleate, Theophylline, Ampicillin, Cinnarazine, Dilitiazem, Florouracil, Prednisolone, Acetaminophen, Verapamil HCI, Amoxycillin trihydrate, and Isosorbide di nitrate and mononitrate.
Capsules	Nicardipine, Chlordiazepoxide HCI, Furosemide, Misoprostal, Diazepam, Propranlol, Urodeoxycholic acid.
Microspheres	Aspirin, Griseofulvin, and p-nitroanilline, Ketoprofen, Iboprufen, Terfenadine.
Granules	Indomethacin, Diclofenac sodium, Prednisolone.
Films	Cinnarizine.

ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEMS:[109]

Featuring stomach retentive behavior, floating dosage systems are a significant technological advancement in drug delivery, providing numerous benefits.

1. Floating dosage forms, including tablets or capsules, can stay afloat in bodily fluids for a prolonged duration, even in an alkaline intestinal environment. FDDS is especially useful for medications like antacids that need to work directly in the stomach.FDDS dose forms help to keep the medication floating in the stomach so that a comparatively better response occurs in cases of diarrhea and aggressive intestinal movement.
2. Acidic substances like aspirin can cause irritation when they come into contact with the stomach lining. To mitigate this, HBS/FDDS formulations can be useful for administering aspirin and similar medications.Ferrous salts and antacids, for example, are among the medications that benefit from the FDDS. enhanced absorption of the medicine due to higher GRT and longer duration of the dose form at the absorption site.
3. Controlled drug delivery helps minimize medication-induced mucosal irritation by ensuring the drug is released gradually and at a steady rate.
4. Management of gastrointestinal conditions, including reflux of the stomach.
5. Improved patient adherence and ease of use.Drug delivery targeted to a specific site.

DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEMS:[110]

1. Floating systems are not ideal for drugs that struggle with solubility or stability in stomach fluids. Because of their substantial first-pass metabolism and good absorption throughout the GI tract, medications like nifedipine would not be good candidates for FDDS due to the possibility of decreased systemic bioavailability from their delayed stomach emptying. Moreover, the use of FDDS is limited for medications that can cause irritation to the stomach's mucosal lining. One drawback of floating systems is that they need an adequate amount of stomach fluids in order for the medication dose forms to float and function properly.
2. These systems also require food to delay gastric emptying.
3. Gastric retention is influenced by various factors such as pH, food intake, and stomach motility. Due to the variability of these factors, predicting buoyancy is challenging. Floating drug delivery systems are not suitable for medications that can irritate or harm the stomach's mucosal lining.

4. Gastric emptying of floating dosage forms in supine individuals can be unpredictable and largely depends on the size and diameter of the formulation. Consequently, administering floating forms to patients right before bedtime is not recommended.

CONCLUSION

Drugs that are absorbed mostly in the stomach, duodenum, and jejunum—the upper portion of the GI tract—benefit further from the FDDS. Prolonged stomach retention of the dose form prolongs the time for drug absorption, which is a highly varied procedure in the gastrointestinal system. For stomach retention, FDDS seems to be a promising technique. Formulating an effective FDDS appears to be a bit of a struggle, and research will likely continue until a perfect solution with practical industrial application is found.

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