

A Panoramic Review on Gastro-Retentive Floating Drug Delivery System

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ABSTRACT

Floating drug delivery has been demonstrated to be the most efficacious of the numerous gastroretentive drug delivery mechanism strategies. The concept behind this system has drawn substantial interest in recent decades. Several strategies are currently implemented to prolong the stomach residence durations, such as floating drug delivery systems, swelling and expansion systems, polymer bioadhesive systems, deformation systems, high-density, etc., systems, and various delayed emptying gastric devices. From a formulation and technology standpoint, floating drug delivery equipment is a rather simplistic and straightforward approach. Floating delivery of drug systems is one of the GRDFs used to increase stomach residence duration. The floating medication delivery device can persist in the gastrointestinal region for several hours due to its floating action on the stomach contents, extensively enhancing the gastrointestinal residence period of drugs. The main thrust of this review is on the design, factors, characterization, applications, evaluation criteria, and prospective future gastro-retentive floating medication delivery techniques.

Keywords: Floating drug delivery technique, Gastric content, Strategies, Applications, Evaluation.

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INTRODUCTION

The drug delivery system has been greatly impacted by medication delivery devices that can accurately control drug distribution rates or deliver drugs to a particular bodily spot. Oral controlled-release dose products have evolved during the previous three centuries because of their significant therapeutic benefits including simplicity of management, patient adherence, and formulation adaptability. Although controlled delivery methods to be administered orally have made significant strides, they have had mixed results when used with medication with a poor GIT absorption window.¹ Modifying the GI transit time is one of the biggest obstacles during manufacturing an oral-controlled medication delivery system. Pharmaceuticals' gastric emptying varies greatly depending on the dosage form and whether the patient is fueled or fasting. Typically, the normal stomach residence periods range from 5 to 2 hours. The gastrointestinal impulses, known as the digestive myoelectric phase or migrating myoelectric complex (MMC), modulate exertion and, thus, the passage of dosage type during fasting. It is distinguished by four factors: Phase I: No retraction duration (40–60 minutes)
Phase II: Intermittent contractions period (20–40 minutes)
Phase III: Also referred to as the housekeeping wave, a

periodicity of consistent contractions at the highest regularity that propagates distantly (10–20 minutes)

Phase IV: Transitional between phase III to I (0–5 minutes) (Figure 1).²

To eliminate *Helicobacter pylori*, chemical substances that have poor absorption inside the decreased part of the GIT, are susceptible and insoluble at alkaline pH, have a brief half lifestyle, and have consequences at the top region of the gut are incredible applicants for gastro-retentive drug delivery system (GRDDS).³ There are multiple scientific techniques. Such as GRDDS, to enhance the stomach retention of a dose form that includes mucoadhesive, high density, expandable, and floating drug delivery system.⁴ FDDES does not negatively impact the gastrointestinal tract (GIT's) motility; hence, they are the subject of substantial investigation. An analogous system intends to extend the gastrointestinal retention of GIT dosing regimens, which will lead to better local bioavailability, therapeutic efficacy, and perhaps even smaller doses and less frequent administration.⁵

Floating Drug Delivery System

As FDDES have a since they have an inferior bulk density than gastric contents, they float for a longer duration without lowering the pace at which the gut empties. The medicine is

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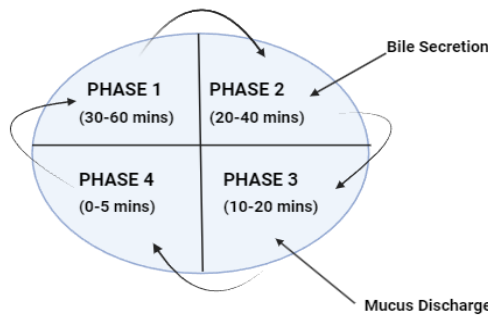


Figure 1: Schematic representation of inter-digestive motility

delivered slowly and at the appropriate speed, whereas the system is suspended. Located in the gastrointestinal tract, once the substance is produced, the system is expelled from the stomach. Consequently, the GIT is enhanced, and variations in blood medication concentrations are better managed.⁶ Patented formulation on the floating drug delivery system as shown in Table 1.

Merits

- Increase in patient adherence by reduced frequency of dose.
- The beneficial effects of medications with short half-lives can be improved.
- Buoyancy expands the period of gastric retention.
- For an extensive period, drugs are released in a regulated way.
- Increased absorption of medications that only dissolve in the stomach.

Demerits

- Unsuitable for medications with issues with solubility or stability in stomach fluid.
- Restrictions on the use of FDDS for medications that irritate the stomach mucosa
- For the dose form to float effectively and maintain buoyancy, a high quantity of fluids must be present in the stomach.⁷

Factor Regulating Gastric Retention of Dosage Form

Density

The fact that the density of the dose form (1.004 g/mL) tends to be lower than that of the gastrointestinal contents.

Size

According to reports, in comparison to dose units with a 9.9 mm diameter, those having a dimension more than 7.5 mm have a higher rate of absorption

Shape

Tetrahedron and circular equipment with versatile modulations of 48 and 22.5 kg² inch (KSI). Compared to other shapes, accumulation ranged from 90 to 100% after 24 hours.

Mono or multi-unit formulation

When contrast to one individual dose emerges, multi unit compositions have a more substantial degree of predictability regarding module failure, allow for the

concurrent administration of modules with various release patterns or holding unsuitable chemicals, and allow for a bigger margin of comfort regarding dosage form failures.

Fed or fasted condition

The intensive motor rotation known as the migration myoelectric compound (MMC), which develops daily halfway through 2 hours, characterizes GI motility while one is fasting. If the formulation is delivered concurrently with the MMC, which evacuates leftover food from the gastrointestinal tract, so therefore the unit's GRT should be appropriately explained. Although, MMC is retarded and GRT is significantly larger in the fueled condition.⁸

Caloric content

When consuming a meal with a lot of proteins and fats, GRT can go up by 4 to 10 hours.

Gender

The average mobility gastrointestinal system of men (3.4 0.6 hours) is smaller compared to individuals of their identical aged and racial female peers (4.6 1.2 hours), despite of size, length, or body region.

Age

oldercitizens have much greater duration GRTs, specifically those over 70.⁹

Types of Floating Drug Delivery System

Two significantly different innovations have been used in the formation of FDDS based on the concept of buoyancy, which are also shown in Figure 2:

- Effervescent process
- Non-effervescent process

Effervescent Process

The effervescent process uses carbonates (such as sodium bicarbonate) and various natural acids (such as citric acid and tartaric acid) that are already implemented into the procedure to generate carbon dioxide (CO₂) gas, which lowers the complexity process causing drift contents of the stomach. The integration of a matrix with a fluid part that produces gas that dissipates the temperature of the body is an alternative.¹⁰

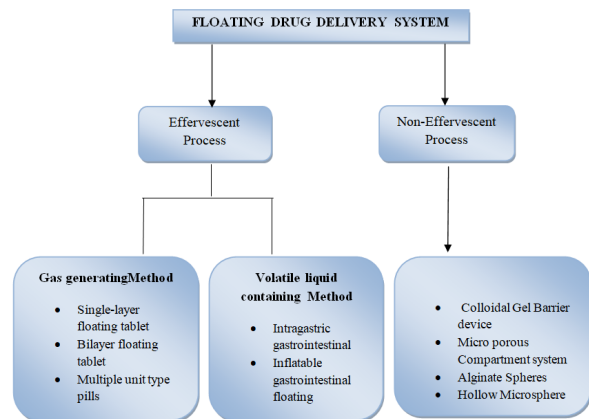


Figure 2: Categorization of floating systems

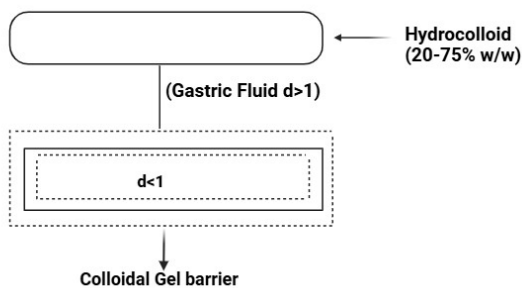


Figure 3: Single-layer floating tablet

The two types of effervescent methods are as follows:

- Gas-generating method
- Volatile liquid Method

Gas generating method

These voluminous delivery methods produce CO₂ by the effervescent processes of citric/tartaric acid and carbonate/bicarbonate salts. Carbon dioxide (CO₂) is subsequently picked up in the gelatinous hydrocolloid. The component surface of the system lowers its gravitation and leads it to drift across gastrointestinal content.¹¹

- *Single layered floating tablets or hydro dynamically balanced system*¹²

These are generated by entirely merging the drug and CO₂ emitters in the matrix tablet. These float round in the gastrointestinal tract for an extended duration of time than gastric fluids since they have a lesser bulk volume, which lowers the pace at which the stomach empties. Any residue medication is drove from the stomach following the desired quantity has been effectively removed from the floating system. As a result, the GRT increases and the variation in serum drug content is more effectively maintained. Figure 3 shown single layer floating tablet.¹²

- *Bi-layer floating tablet*

A bi-layer tablet contains two layers: An immediate-release layer that expels the first dose from the body and an extended-release layer that accumulates gastrointestinal secretions and solidifies into an impenetrable colloidal gel membrane on the surface also shown in Figure 4. Maintaining a mass density that is less than unity, these layers work together to keep a bi-layer tablet buoyant in the GI tract.¹³

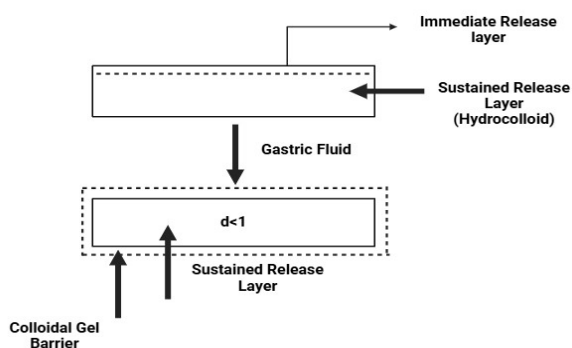


Figure 4: Bi-layer floating tablet

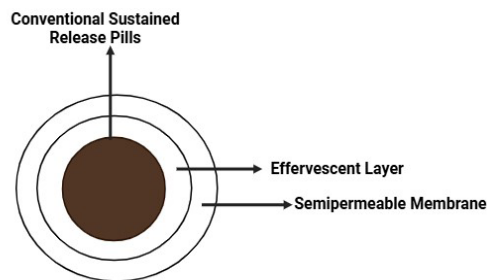


Figure 5: Multiple unit type pills

- *Multiple unit type pills*

This framework is composed of two layers that surround prolonged-release capsules that serve as “seeds.” The external layer is made up of an expandable layer, and the primary surface is made up of effervescent substances shown in Figure 5. When immersed in a media that dissolves at body temperature, the system rapidly lowers and produces larger tablets that float because of their lesser strength and simulate bubbles. The creation and entrapment of CO₂ within the systems is the cause of this decreased density.¹⁴

- *Floating system with ion exchange resins*

Ion-exchange resins, an oral buoyant dosing system with several units, have been created to postpone the period of the dose form spent being evacuated from the gut. Particles made of drug-resin combination that have hydrophobic polymer coatings and are bicarbonate ion-loaded make up the system. When the particles reach the stomach, the process is set up so that chloride ions are switched out for bicarbonate and medication ions. The created CO₂ is captured by the coated resin with polymer compounds, which leads the particles to float.¹⁵

Volatile liquid containing system

- *Intra gastric gastrointestinal floating system*

Some devices can be intended to drift in the gastrointestinal tract due to the floating chamber, which can be a void composed of air or loaded with an innocuous chemical shown in Figure 6. The drug repository is contained within a tiny pore chamber.¹⁶

- *Inflatable gastrointestinal floating system*

These structures use an inflatable container comprising liquid ether that, when elevated to human temperature, vaporizes, and causes the causes to expand inside the stomach. To create these methods. A matrix of polymeric materials infused with a drug is put inside an inflated chamber, which is then contained in a gelatin vial. Capsules disintegrate after oral administration, producing the drug repository and the expanded container. Automatically, the inflatable chamber expands and enters the gastrointestinal fluid.¹⁷

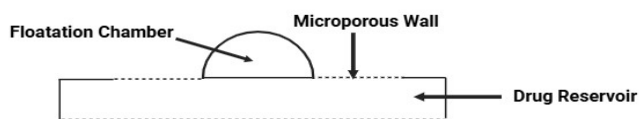


Figure 6: Intra gastric gastrointestinal floating device

Non-effervescent System

Non-effervescent FDDS relies on an adhesiveness to the mucosal layer of the intestinal tract or a polymer-swelling mechanism. Hydrophilic gums, polysaccharides, gel-forming or extremely swellable viscous form hydrocolloids, matrix-making materials including polycarbonate, polyacrylate, polymethacrylate, polystyrene, and bioadhesive polymers like chitosan are the most often used ingredients in non-effervescent floating drug delivery process.¹⁸ The following are the several types of these systems:

Colloidal gel barrier system

Sheth and Tossounian first referred to this gadget as a “hydrodynamically balanced gadget”.¹⁹ These devices contain drugs that gel-form hydrogels, enabling them to float on stomach contents. This extends GRT and raises the strength of the drug in solution form at the absorption sites for fast absorption. High levels of polysaccharides, matrix-forming chemicals like poly-carbophilic, polyacrylate, and polystyrene, and one or more cellulose-type hydrocolloids that form highly soluble gels, like hydroxyl propyl cellulose are present in this system. This hydrocolloid absorbs and generates a barrier of colloidal gel on its interface., when in correspondence with stomach acid assisting in the prolonged release of medicines.

Micro porous compartment system

A microporous compartment that contains a drug reservoir on this device has perforations on the edges, both upper and bottom.²⁰ There is complete sealing of the medication reservoir compartment’s exterior walls. This sealing keeps the undissolved medication from coming into contact with the stomach’s mucosa. The floating chamber, which has air trapped inside of it, allows the delivery method to drift above the gastric mucus of the GI tract. Gastrointestinal fluid passes through an opening, dissolves the drug, and constantly conveys it across the intestinal tract for absorption.²¹

Alginate spheres

Freeze-dried calcium alginate was exploited to manufacture multi-unit floating dose formulations. An aqueous mixture of calcium chloride is formed by merging a sodium alginate solution with it. Calcium alginate precipitates and forms a perforated structure capable of maintaining a floating pressure for longer than 12 hours. This method can be used to create circular beads ranging in size from around 2.5 mm. In contrast to firm beads, which only provided a dwelling period of one hour, these floating beads provided a dwelling period of more than 5.5 hours.²²

Hollow microspheres

A distinctive technique was implemented to fabricate hollow spheres (microballoons) that were filled with drugs and had outside polymeric shells shown in Figure 7. The method is using diffuser-emulsion interaction. The drug’s ethanol: dichloromethane mixture was added to an agitated, 40°C-controlled aqueous PVA solution along with an enteric acrylic polymer invitro, and the microscopic balloons floated

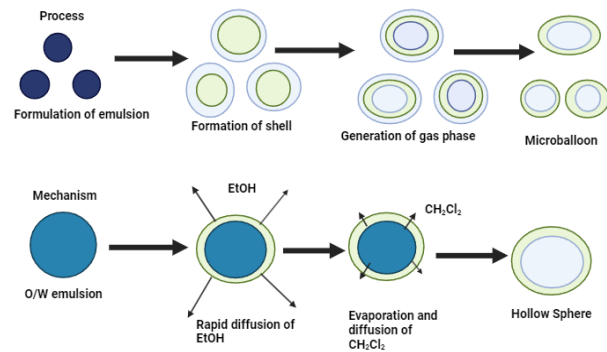


Figure 7: Hollow microspheres

continually across the surfactant-containing, acid-dissolving medium for more than twelve hours.²³

Evaluation Parameter of Gastro Retentive Floating Drug Delivery System

The derived formulations’ physicochemical parameters and release characteristics were evaluated.

Pre-compression studies

- *Angle of repose*

By evaluating the angle of repose, one can determine the friction force present in fine powder or the particles. The surface of a mound of powders or granules can only be angled away from the symmetrical by this amount. The particles were allowed to tumble down a funnel that was mounted to a platform at a particular elevation. After that, the elevation and diameter of the resulting pile of particles were evaluated to determine the inclination of repose.²⁴

- *Carr’s index*

Analyzing the predominant density (ρ) and tap density (ρ_t) of the powder and the velocity of the powder collapses and allows one to assess the flow ability of the substance.

The Carr’s index can be determined as:

$$\text{Carr's index (\%)} = \frac{\rho_t - \rho}{\rho_t} \times 100$$

Where, ρ = Bulk density g/ml002E

ρ_t = tapped density g/mL

Post-compression studies

- *Shape of tablet*

Under a magnifying glass, compressed pills were checked for the tablet’s shape. The width and dimension were determined with a graded vernier caliper. Three tablets from each composition were opted spontaneously, and each tablet’s thickness was analyzed.²⁵

- *Hardness*

The degree of a tablet’s hardness determines how well it can endure handling mechanical shocks. The tablets were evaluated for hardness using a Monsanto hardness tester. It was stated

in kg/cm^2 . A random sample of three tablets was chosen, and their hardness was measured.²⁶

- *Friability test*

The friability of the tablets was evaluated using a Roche Fabricator. It was expressed in percentages. Ten capsules were first weighed (initial W) and placed in a frit. The friability test was changed to be performed at 25 rpm for four minutes or up to 100 rpm.

- *Tablet density*

Tablet density was a key factor in floating tablets. Only when the density of the tablet was lower than that of the gastrointestinal secretion (1.004) did the tablet levitate. Simulations were determined using the algorithm provided the density:²⁷

$$V = r2h \quad d = m/v$$

- *Weight variance test*

To verify weight variance, 10 tablets were randomly selected from every group and estimated separately. The U.S. Pharmacopoeia permitted a small amount of variation in tablet weight.²⁸

- *Buoyancy or floating test*

Chronograph devices were used to measure how long the dosage form remained buoyant before getting inserted into the fictitious gastrointestinal fluid. The time required for the dose form to appear on the medium's surface is referred to as the floating lag time (FLT) or buoyancy lag time (BLT), and the complete amount of period that remains buoyant is referred to as the total floating time (TFT).²⁹

Characterization Parameter

Size and shape

Scanning electron microscopy (SEM) is used for dimensional and morphological study, and optical microscopes can also be used to evaluate size.³⁰

Surface morphology

Surface morphology and components were detected using a scanning electron microscope, a touch angle meter, a microscope equipped with atomic force microscopy (AFM), and an interface profile meters at an accelerated voltage of 10 kv.³¹

Determination of moisture content

Water itself rarely attracts attention on its own. Instead, it appears that a result presumed for commerce and production contains typical characteristics such as

- Microbiological stability
- Dry substance content
- Concentration or purity
- Storability
- Agglomeration in case of powders³²

Thus, the moisture level of the produced formulations was evaluated using physical and Karl Fisher titration techniques. Steam drying, using thermal gravimetric techniques, the air oven process, measuring moisture, and freeze-drying.³³

Swelling studies

This is carried out to figure out the molecular properties of swelling polymers. It is assessed using microscopy with optical fibers and a dissolving instrument and other cutting-edge methods like confocal laser scanning microscopy (CLSM), light scattering imaging, and ¹H-NMR imaging. The following formula is used to compute the dissolution apparatus.³⁴

Percentage entrapment efficiency

Percentage of defense for assessing the drug component distribution within the ready formulations, efficacy was a reliable measurement. Utilizing small qualitative analysis methodologies, excessive activity, and pressure-immoderate filtering, resistance potency is assessed.³⁵

Drug content analysis

The total quantity of the drug that was incorporated in the composition is indicated by the drug content percentage. It must stay within the bounds established by conventional monographs. Spectrometer for inductively coupled plasma atomic emission (ICPAES), near-infrared spectroscopy (NIRS), titrimetric methods, and spectroscopy techniques were all used to determine the drug content.³⁶

In-vitro drug release

Using a dissolving apparatus, dissolution tests are conducted. Samples are constantly taken out of the dissolution media and refilled, and when an appropriate dilution is present, their drug content is examined.³⁷

Fourier-transformed infrared analysis

The method used to determine natural, polymeric, and certain chemical compounds as well as for deliberate cluster identification is Fourier-transformed infrared (FTIR) qualitative analysis.³⁸ FTIR measurements were performed on the natural drugs, polymers, and drug-infused polymer compositions. The spectrum was detected over the wave number range of 3600 to 400 cm^{-1} while pellets were at room temperature using a KBr-press with a 150 kg/cm^2 hydraulic force.³⁹

Power X-Ray diffraction

The X-ray powder visual condition is the most prevalent instrument investigating compounds perfectly suited for regular assessment of pharmaceutical products. The instances were exposed to irradiation and then were to between 2 and 6°C for analysis. 30 KV and 30 mA were the employed voltage and current, respectively.⁴⁰

Differential scanning calorimetry

Model-DSC-60/DSC-50/Metler from Shimadzu Toledo is typically used to describe the hydration water for medications. Thermograms of prepared materials were measured through a DSC device with an intercooler. Utilizing indium/zinc standards, the DSC temperature and entropy scales were calibrated. The sample preparations were heated from 25 to 65°C at a continuous rate of $10^\circ\text{C}/\text{min}$ while being hermetically enclosed in an aluminum pan.⁴¹

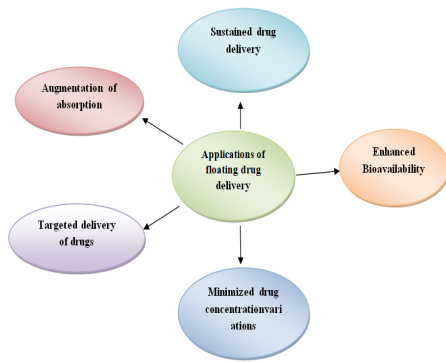


Figure 8: Applications of floating drug delivery system

Applications of Floating Drug Delivery System

Applications of floating drug delivery system shown in Figure 8:

Sustained drug delivery

Oral CR preparations experience difficulties such as gastric region duration in the stomach. These issues can be resolved with HBS mechanisms, which can persist in the gastrointestinal tract over extended spans of time and have a substantial bulk volume that allows them to float atop the gastric mucus. These networks are significantly bigger in shape, and passage from the pyloric hole is prevented.⁴²

Augmentation of absorption

A drug with minimal accessibility due to a Particular site of administration from the top portion of the gut, which can enhance their absorption, is a potential candidate for floating drug delivery systems.⁴³

Targeted delivery of drugs

These applications are particularly effective for drugs that predominantly uptake through the gastrointestinal tract or the

first region of the small intestine,⁴⁴ a regulated, progressive delivery of the medication results in acceptable local doses while minimizing systemic exposure. As a result, the drug’s drawback consequences on blood perfusion are reduced. Moreover, a site-specific administration method could lower the dose frequency because of the prolonged gastrointestinal availability, e.g., furosemide and riboflavin.⁴⁵

Enhanced bioavailability

The bioavailability of riboflavin CR-GRDF is much better compared to control polymer formulations of riboflavin CR without GRDF. Numerous interconnected processes that occur simultaneously in the gastrointestinal tract during drug absorption and transit affect how much medication is absorbed.⁴⁶

Minimized drug concentration variations

Plasma drug levels are produced by continuing to provide the drug after CRGRDF delivery. Compared to the dose forms for instant release, within a smaller range. As a result, drug effects vary less often, and adverse effects that depend on dosage and are correlated with elevated levels can be excluded. This characteristic is very significant for drugs with a low therapeutic efficacy.⁴⁷

Drugs that are stable in acid, those that are insoluble or unstable in gastrointestinal fluids, and those that exhibit drastic variations in their pH-related solubility as an outcome of diet, aging, and pathologic states of the GIT can all benefit from floating systems. For instance, a floating system for furosemide could be used in the rehabilitation of Parkinson’s disease.⁴⁸

Future Prospects

Floating drug delivery is a promising strategy that has emerged as a critical component of forthcoming studies. Drugs with inadequate bioavailability due to reduced absorbance in the top gastrointestinal tract are given productively through the

Table 1: Patented formulation on the floating drug delivery system

S. No.	Patent number	Type of formulation	Approach	Year	Ref.
1.	US 5626876	Floating system for oral therapy	The innovation pertains to an oral therapy device that can drift on gastric fluid and is only just able to reach the lower-lying pylorus since it is substantially lighter than that fluid.	1997	52
2.	US 6207197	Gastro-retentive controlled release microspheres	This approach consists of an inner microsphere comprising an active ingredient and a rate-regulating layer comprised of water-resistive polymers.	2001	53
3.	US 8277843	Programmable buoyant delivery technology	This technique included a center, single or multiple layers that were drug-coated around the core, and a hollow space that was already constructed. This technology offered configurable drug delivery in both space and time.	2012	54
4.	US 8808669	GR extended-release composition of the therapeutic agent	The technique involves a controlled-release formulation that can float and swell at acidic pH and distribute the drugs over an extended duration of time.	2014	55
5.	US 9314430	Floating GR dosage form	The technique uses an opposed dose form with two cylinder ends that float because of its peculiar size and shape.	2016	56
6.	US 9561179	Controlled release floating pharmaceutical compositions	The current innovation included several controlled-release coated microparticles with drugs placed on their surfaces, along with a controlled-release coating.	2017	57

floating delivery strategy. However, there are a few drawbacks linked to rational development FDDS in the fasted and fed phases that must be addressed.⁴⁹ Combination therapy to cure *H. Pylori* infection in a single FDDS is required. Further research could focus on the following concept:

- Development of new polymers in alignment with clinical and pharmaceutical requirements.
- Development of a variety of FDDS, each with a limited GRT for use based on scientific requirements, such as dose and illness stage. This can be accomplished by combining polymeric dimensions with different biodegradation properties.
- Identification of a minimum threshold size above which DFs can be maintained in the human intestine over an extensive duration of time. This would allow for more reliable supervision of gastro retentivity.⁵⁰
- Analyzing the impact of posture on the efficacy of floating dosage forms that contain one unit versus many units whether consumed before or after a meal.⁵¹

CONCLUSION

Prolonging gastric retention of the dosage form causes drug absorption to take more time. The administration of drugs in the gastrointestinal tract is an intricate process. FDDS can alleviate GI retention. These systems assist in the constant release of the drugs before they reach the absorption window, upholding excellent bioavailability. FDDS seems to be an intriguing gastric retention approach. Despite the obstacles that must be addressed to achieve extended gastro retention, different companies are focusing on commercialization.

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