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ADVANCING DRUG DELIVERY: UNVEILING THE POTENTIAL OF GASTRORETENTIVE SYSTEMS

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ABSTRACT

There have been numerous initiatives in recent years to increase drug absorption rates and the therapeutic effectiveness of oral dosage forms. By employing gastroretentive drug delivery systems, it is possible to overcome the major drawbacks of conventional drug delivery methods, including their short residence time, unpredictable absorption, and lack of control over drug release. These systems are useful tools for enhancing medication therapy because they have the potential to increase drug absorption, bioavailability, patient compliance, and consistent therapeutic effects. One of these methods for extending gastric residence time is gastroretentive drug delivery, which targets site-specific drug release in the stomach for local or systemic effects. The distinct evaluation criteria for the gastroretentive systems vary depending on the dosage types. The selection of a drug for use in gastro-retardant systems must meet a number of requirements, including restricted absorption, sparingly stability, and compatibility with the gastrointestinal region. In addition to discussing the synthetic polymers utilized in the formulation and marketed products, this review emphasizes the numerous pharmacological strategies for gastroretention such as floating drug delivery systems, mucoadhesive systems, high-density systems, expandable and swelling systems, ion exchange resin system and recent patents filed or granted for this approach.

KEYWORDS: Gastroretentive, Bioavailability, Polymers, Floating drug delivery, Gastric residence time.

INTRODUCTION

The oral route is the most effective way to administer drugs for single-dose systems since it is simple to use, easy to administer, and inexpensive to manufacture single dosage controlled release systems or extended or sustained release dosage form. Numerous studies have been conducted to improve patient compliance and prevent the need for drug administration more than once, Low solubility at pH levels greater than 7 and high solubility at acidic pH conditions led to a narrower medication absorption window from the intestine. One method for extending gastric residency time is gastro retentive drug delivery(GRDD), which targets site-specific drug release in the stomach for local or systemic effects. Long-lasting in the gastric region, these dosage forms greatly extend the duration that medications are retained in the stomach. In order for the drug to be continually given to the stomach's absorption location in the GIT, it will release the medication into the stomach in a controlled manner.[1] As a result, various strategies have been suggested to keep the dosage form in the stomach. These consist of low density super porous systems, floating systems, bio adhesive systems, swelling, expanding, and delayed gastric emptying systems.[2] For medications that are absorbed from the stomach (such as albuterol), are labile at alkaline pH (such as ranitidine and metformin), are poorly soluble at alkaline pH (such as furosemide and diazepam) or have a limited window of absorption (such as riboflavin and levodopa), GRDDS are an appropriate alternative.[3] Enhancing bioavailability and having site-specific medication delivery are the main benefits of GRDDS for treating GI disorders. When drug bioavailability is enhanced, dose repetition is reduced, which minimizes GI disturbance, compared to conventional dose forms, the GRDDS has the drawback of being incompatible with drugs that irritate the gastrointestinal mucosa.[4]

PHYSIOLOGY OF STOMACH

The gastrointestinal tract, which includes the throat (pharynx), oesophagus, stomach(**figure 1)**, small intestine (consisting of the duodenum, jejunum, and ileum), and large intestine (consisting of the cecum, appendix, colon, and rectum), is essentially a nine-meter-long tube that runs through the middle of the body from the mouth to the anus. The gastrointestinal tract's wall shares a common overall structure for the most of its length, from the oesophagus to the anus, with significant local variances. An organ having storage and mixing

capabilities is the stomach. The antrum is where the contents of the stomach are mixed and ground. The migrating motor complex (MMC), which is the term used to describe the inter-digestive motility pattern, is structured into cycles of activity and quiescence. Each cycle comprises four phases and lasts 90–120 minutes. The length of the phases is determined by the amount of the hormone motilin in the blood. An MMC wave travels from the stomach through the GI system every 90–120 minutes in the inter-digestive or fasting state. Four phases make up a complete cycle; they start at the lower oesophageal sphincter/gastric pacemaker, spread throughout the entire stomach, the duodenum and jejunum, and end at the ileum. The third phase is known as the "housekeeper wave" because its strong contractions tend to clear the stomach of its indigestible waste and fasting-related contents. The MMC cycle is abruptly broken by the administration and subsequent intake of food, allowing the digestive phase to proceed. The meal is initially stored in the upper section of the stomach, where it is gradually squeezed by phasic contractions. In reaction to a meal being consumed, the digesting or fed state is seen. It resembles the fasting Phase II and is continuous rather than cyclical as long as food is still in the stomach. During the feeding pattern, the stomach retains large things, but Phase III of the inter-digestive MMC allows them to pass. It is believed that the feeding pattern or the presence of food improves the stomach's sieving efficiency (i.e., its capacity to crush food into smaller pieces).[2]

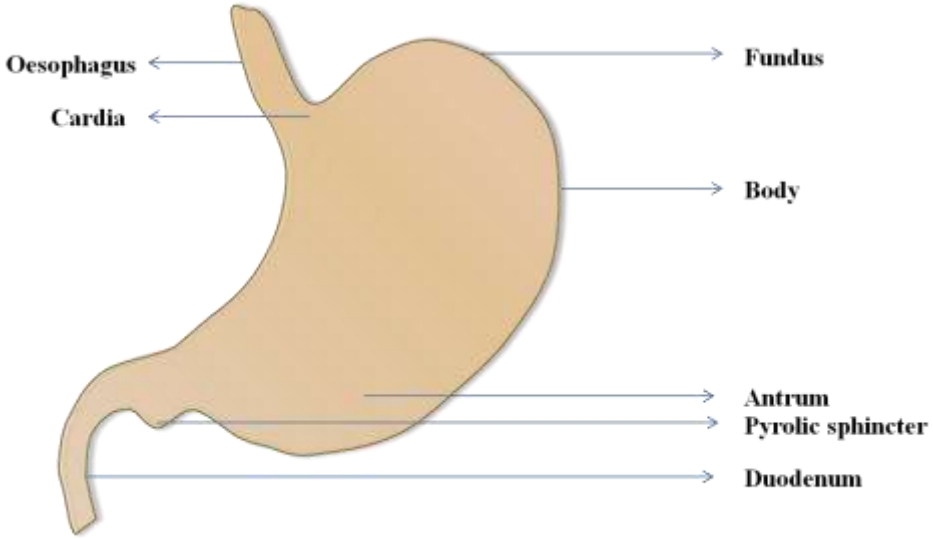

Figure 1: Physiology of stomach.

Composition of gastric content

The stomach has a 1.12–1.5 L capacity and a normal stomach has a J shape. The fundus area, which makes about 60–80 percent of the entire mucosal surface, is the largest portion of the stomach. The lower curvature angle forms known as Incisura angularis divide the bottom half of the fundus zone from the pylorus. The transitional zone, also known as the interface of the pyloric and fundus regions, is where the circular fiber of the pyloric sphincter protects against the backflow of small intestinal contents into the stomach. 15% of the overall mucosal region is made up by the pyloric antrum, which is divided into two parts. The pyloric canal, a wider, closer chamber, and the short (approximately 3 cm) pyloric sphincter are where the narrow tubular tube finishes. The napping stomach's pH varies from 1.7 in young adults to 1.3 in older ones. The average stomach produces 3 L of fluid per day, mostly in the form of mucus, lipase enzyme, pepsinogen, acid, and intrinsic factors, mostly from gastric secretion. Parietal cells produce the acids that keep the stomach's pH in the fasted state between 1 and 3.5. Gastrin hormone, a powerful regulator of the production of stomach acid. The pepsinogen precursor of the pepsins produced by the peptic cells. The stomach mucosa is lined with mucus that is produced by the surface mucosal cells.[5]

Function of stomach

The fundus, which makes up the majority of the stomach, is joined by the body and antrum. Fundus and body handle storage, whereas the antrum is responsible for food crushing and filtering. There are no gastric pits in the mucosa-only stomach.[6]

Migrating myoelectric complex (MMC) cycle

Gastric emptying is observed in both fed and fasted conditions. The motility pattern does, however, differ. The fasting condition differs noticeably from the other two situations in that it is characterized by an inter-digestive 4 phase.

Phase 1: With only sporadic contractions, it is a 40–60 minute period of relative inactivity.
Phase 2: Phase 2 has an identical duration to phase 1 and includes an increasing number of contractions.
Phase 3: After opening the base of the pylorus, this is characterized by powerful peristaltic contractions that rid the stomach of any leftover material.

Phase 4: Between the important acts of phase 1 and phase 3, there is a brief transitional period. Every two hours, the procedure is carried out again, up until the meal is ingested and provided, or motility starts.[7]

COMPARISON BETWEEN CONVENTIONAL DOSAGE FORM AND GRDDF

Table 1: Comparison between GRDDF & Conventional.

S.no.	Feature	GRDDF	Conventional DF
01	Patient compliance	Improved patient compliance	Less
02	Drugs with rapid absorption through GIT	Highly beneficial	Not much beneficial
03	Chances of adverse effects	Low risk	High risk
04	Narrow absorption window in the small intestine	Useful	Not useful
05	Colon degrading drugs	Highly beneficial	Not much beneficial
06	Poorly soluble drugs in alkaline pH	Highly beneficial	Not much beneficial
07	Locally acting drugs in the stomach	Highly beneficial	Not much beneficial
08	Dose-dumping risk	Low risk	High risk

ADVANTAGES OF GRDDS

- Increased bioavailability: The bioavailability of medications like riboflavin and levodopa, which are absorbed in the upper section of the GIT, has significantly enhanced compared to that of conventional dosage forms.
- Lower dosage frequency and sustained drug release. Thus, patient compliance is enhanced.
- Targeted drug delivery at the upper GIT makes it appropriate for the local treatment of the disease in the area, such as antacids, anti-ulcer medications, and antibiotics for H. pylori infection.
- Suitable for medications including furosemide, captopril, diazepam, verapamil, and cefpodoxime proxetil whose stomach absorption is pH dependent.
- Suitable for medications like ranitidine hydrochloride that break down in the intestine or bile duct.
- Over a long length of time, there is no drug level fluctuation and the ideal therapeutic plasma and tissue concentrations are maintained. This reduces the chance of medical treatment failure and unfavourable side effects and avoids sub-therapeutics and hazardous concentrations.

DISADVANTAGES OF GRDDS

- Drugs that are unstable in an acidic environment should not use it.
- It is not appropriate for medications whose absorption is enhanced in the lower GIT region.
- Having trouble getting the required results and a dose dumping issue.
- Numerous elements, including stomach motility, pH, and the presence of food, might affect gastric retention. Therefore, the dose form needs to be strong enough to survive the stomach's peristaltic wave's churning and grinding action.
- Poor *in-vitro* and *in-vivo* correlation.
- Higher formulation costs.
- In cases of toxicity, poisoning, or hypersensitive reaction, drug retrieval can be challenging.[8]

POLYMERS AND OTHER EXCIPIENTS USED IN FORMULATION OF GRDDS

Table 2: polymers and excipients are listed below.

CATEGORY	MATERIALS
Polymers	HPMC K4M, HPMC K100, calcium alginate, CMC, Eudragit RL, Eudragit S100, Eudragit RS, polyethylene glycol, B cyclodextrin.
Inert fatty material (5-75%)	Edible inert materials having a specific gravity less than 1 can be used to decrease hydrophilic property of formulation and hence increase buoyancy e.g., bees wax, fatty acid.
Effervescent	Sodium bi carbonate, citric acid, tartaric acid
Release rate accelerants (5-65%)	Lactose, mannitol
Release rate retard (5-60%)	Talc, magnesium stearate, di calcium phosphate
Buoyancy increasing agent (up to 80%)	Ethyl cellulose
Low density material	Propylene foam powder

CLASSIFICATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

To enhance the retention of oral dosage forms in the stomach, a variety of gastrointestinal pharmaceutical administration techniques have been tested. While some dosage forms are multi-component formulated, others are single component produced. GRDDS can be broadly

classified into floating and non-floating systems as depicted in **Figure 2**.

FLOATING SYSTEMS

EFFERVESCENT SYSTEM

These systems are of the matrix kind. Prepared with the use of several effervescent chemicals and swellable polymers, including methylcellulose and chitosan. Ex: citric acid, tartaric acid, sodium bicarbonate. These are designed in such a way that when they come into touch with gastric contents, CO2 is released and captured in swelling hydrocolloid, giving the dosage form buoyancy. The swellable asymmetric triple layer tablet technique served as the foundation for the delivery system's design.[9] These systems can also be categorized as follows.

Gas generating system

This system's primary mechanism involves the reaction between sodium bicarbonate, citric acid, and tartaric acid, which results in the formation of CO_2 gas. The gas created causes the system's density to decrease, causing it to become less dense and float on the stomach contents. Salts and citric/tartaric acid release CO_2, which gets trapped in the system's jellified hydrocolloid layer, causing its specific gravity to drop and it to float over the chime. A sustain release pill serves as the system's seed, and two layers surround it. The inner layer is an effervescent layer made of tartaric acid and sodium bicarbonate. A swellable membrane layer with PVA, shellac, and other materials makes up the outer layer.[10] It is further broken down into:

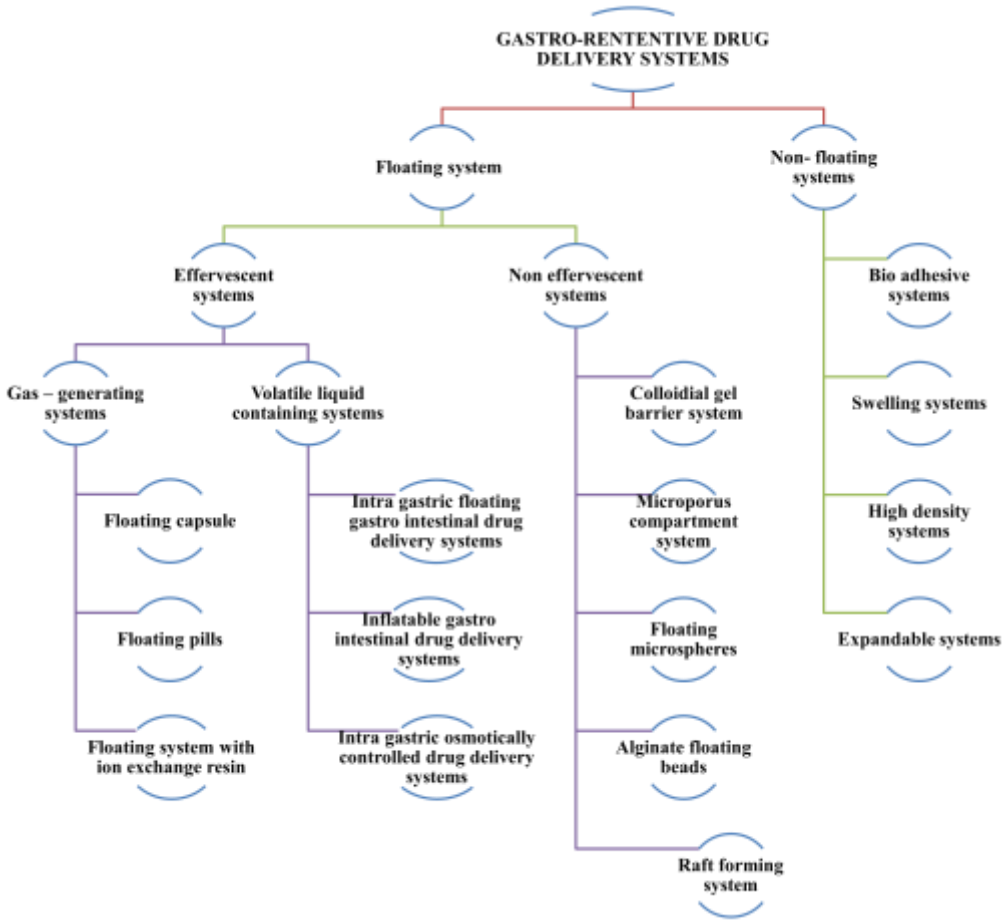

Figure 2: Classification of GRDDS.

Floating capsule

The preparation of these involves creating a solution of sodium bicarbonate and sodium alginate. When in an acidic environment, CO_2 gas is produced, which is captured in the network of hydrating gel and causes the system to float.

Floating pills

These fall under the category of sustained release formulations, which are essentially various forms of unit dose. There are two layers surrounding the sustained release pill. Swellable membrane makes up the outside layer, and effervescent agents make up the inner layer. Due to a swellable membrane, the systems first swell before sinking. The system floats as a result of the effervescent agent's presence since it releases CO_2.

Floating system with ion exchange resin

The most typical method for creating these systems is resin beads that have been loaded with bi carbonates. Ethyl cellulose, which is typically insoluble but

permeable to water, is then layered on top of this, causing carbon dioxide to leak and the system to float.

Volatile liquid containing system
These have an inflatable chamber with a liquid within, such as ether or cyclopentane, which gasifies at body temperature and causes the chamber in the stomach to inflate. These systems consist of a hollow deformable unit and are osmotically controlled floating devices. The system consists of two chambers, the first of which holds the medicine and the second of which holds the volatile system. They are categorized as.

Intra gastric floating gastrointestinal drug delivery system
This method includes a flotation chamber that is vacuum-filled or filled with a safe, inert gas, as well as a microporous compartment that houses the drug reservoir.

Inflatable gastrointestinal drug delivery system
The stomach is inflated by these devices inflatable chambers, which contain liquid ether and gasifiers that operate at body temperature. The bio-erodible polymer filament used in inflatable chambers, such as copolymers of polyvinyl alcohol and polyethylene, progressively dissolves in gastric fluid before causing the inflated chamber to release gas and collapse.

Intra-gastric osmotically controlled drug delivery system
It consists of an inflatable floating capsule and a drug delivery system regulated by osmotic pressure. The osmotically regulated drug delivery system, which consists of two parts: a drug reservoir compartment and an osmotically active compartment, is released when the inflatable capsule ruptures in the stomach.[11]

NON- EFFERVESCENT SYSTEM
Hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polystyrene, and polymethacrylate are employed in this type of floating GRDDS. These are additionally categorized as follows.

Colloid gel-based system
Sheath and Tossounian created the Hydrodynamically Balanced System (HBS) in 1975, which includes medications with hydrocolloids that produce gels. These systems have a high concentration (20–75%w/w) of one or more hydrocolloids of the cellulose type that produce gels and are highly swellable, as well as polysaccharides and matrix-forming polymers. The hydrocolloids in the system hydrate and create a colloidal gel barrier on the surface of stomach fluid when they come into contact with it. This gel barrier regulates how quickly fluids enter the device and release the medicine as a result.[12]

Microporous compartment system
This device works by enclosing a drug reservoir inside a tiny, porous space that has perforations running the length of its top and bottom walls. To avoid any direct drug interaction with the gastric mucosal surface, the periphery of the drug reservoir compartment is entirely sealed.

Floating microspheres
The core hollow region within the microsphere makes hollow microspheres the most favorable buoyant system, according to experts. A unique emulsion solvent Diffusion approach was used to create hollow microspheres that are loaded with medication in their outer polymer shelf.[12]

Alginate floating beads
Freeze-cured calcium alginate has been used to create multi-unit floating dosage forms. By adding sodium alginate solution to aqueous calcium chloride solution, spherical beads with a diameter of around 2.5 mm can be created. causing calcium alginate to precipitate. After being separated, the beads are quickly frozen in liquid nitrogen and then freeze-dried at 400°C for 24 hours, creating a porous structure that can sustain a floating force for more than 12 hours. The prolonged residence length of these floating beads was greater than 5.5 hours.

Raft forming system
For the delivery of antacids and drugs for gastro infections and diseases on contact with stomach fluid, raft forming systems have drawn a lot of interest. A solution that generates gel expands and transforms into a thick, cohesive gel that traps CO_2 bubbles. which creates a raft layer on top of the gastric fluid, releasing the medicine gradually into the stomach. (Frequently used to treat gastroesophageal reflux disease).

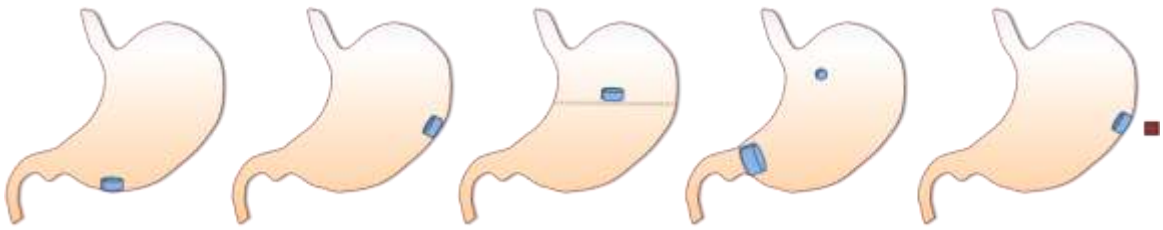

Figure 3: a) High density systems; b) Bio-adhesive systems; c) Floating systems; d) Expandable systems; e) Magnetic systems.

Magnetic system

This system regulates the movement of the gastroretentive formulation with a small internal magnet by applying a strong magnet with a strong magnetic field onto the body surface. The success of this system hinges on the extremely precise selection of the magnet position, as seen by the numerous testimonials that witness to its favourable outcomes. The internal magnet-equipped peroral acyclovir depot tablets were created. In order to extend the GRT of the dosage form and affect the amount of time that acyclovir is absorbed, an extracorporeal magnet was used. Five healthy male individuals participated in an *in-vivo* investigation to investigate the plasma concentration-time profiles of acyclovir. Acyclovir depot preparations effects on the plasma concentration-time profiles were visualised using computer simulations.[13] A GRDDS magnetic system is shown in **Figure.3.**

NON-FLOATING SYSTEM

Despite not floating in the stomach, these GRDD devices are kept there by several mechanisms.

Bio adhesive system

These kinds of systems stick to the stomach's mucosa, the biological membrane, and keep close touch with it for a longer period of time, retaining in the stomach for its protracted release. Bio adhesive polymers are used in the formulation of these systems.[14]

Swelling system

These are an assortment of non-floating GRDDS that, when entering the stomach, enlarge to such an extent that they are unable to pass through the pyloric sphincter, causing retention in the stomach.

High density system

These systems have a denser composition than gastric fluids, which causes them to sink to the bottom and stay inside the stomach. These are created by coating drugs with strong inert substances, such as zinc oxide, titanium dioxide, iron powder, etc.

Expandable system

These systems have the capacity to expand and stay in the stomach for prolonged periods of time. These are often made in the shape of folded, compressed capsules that hold the dosage. The dose form expands, and the capsule shell disintegrates in the stomach, making it impossible for it to pass through. Drug distribution that is maintained and under control can be accomplished by employing the right polymer.[15]

CHARACTERIZATION OF GRDDS

Drug-excipient interaction

DSC, FTIR, and HPLC are used in the process. Drug-excipient compatibility was investigated using a DSC analysis. DSC equipment was used to analyze a pure sample of the medication, the excipients, and their physical combinations. An interaction between the drug and excipient is indicated by the emergence of a new peak and/or the removal of the initial drug or excipient peaks.

Total floating time

Total floating time, also known as flotation time, is the amount of time the dosage form floats.

Floating lag time

The period of time between the tablet's introduction to the medium and its ascent to the upper third of the dissolution vessel is known as the floating lag time.[16]

Weight variation

Pharmacopoeias propose using a number of formal techniques to figure out the weight variation. Typically, the weight of each tablet and the average weight of 20 tablets are noted. The average weight and weight variation are computed using these data.

Hardness and friability

A Monsanto tester, Strong Cobb tester, Pfizer tester, etc. are used to measure hardness or crushing strength. A Roche friabilator is used to assess the friability (strength) of tablets.[17]

***In-vitro* drug release and duration of floating**

It is determined by swirling simulated gastric fluid with a pH of 1.2 using a USP II equipment (paddle) at a speed of 50 or 100 rpm at 37°C. Samples are taken in aliquots, which are then examined for drug content. The length of the floating time is the amount of time the medication floats on the medium's surface.[18]

Swelling index

The tablets are submerged in 0.1 N HCl at 37°C and periodically removed to calculate the swelling index.[19]

Water uptake study

The process involves submerging the dosage form in simulated stomach fluid at 37°C and monitoring the changes in the dosage form's dimensions over time, such as changes in diameter and thickness. The enlarged tablets are weighed after the allotted time and the amount of water absorbed is expressed as a percentage weight gain, as follows.

$$W_U = (W_t - Wo)\ X100/Wo$$

Where,

Wo and Wt = weight of the tablet at the beginning and after time t.

Specific gravity/density

Both low-density and high-density GRDDS require precise predictions of specific gravity. The displacement method is employed in the calculation of specific gravity.[20]

Evaluation of microsphere and beads

The particle size of beads and microspheres was measured using an optical microscope. Using a scanning

electron microscope, the morphology of surfaces and cross-sections is assessed.[21]

***In-vivo* evaluation of gastric retention**

Imaging methods like X-rays and γ-scintigraphy are used to examine the dosage form's location in the GIT. When creating the dosage forms for γ-scintigraphy, a little quantity of a stable isotope is compounded. A formulation with a beta-emitting radionuclide enables indirect external observation with a scinti scanner or γ-camera. Barium sulphate is used as a contrast media for x-rays.[22] Locating a dosage form in the GIT makes it easier to predict and correlate the passage of the dosage form and gastric emptying time. Additionally, tests using gastroscopy and ultrasonography may be incorporated into the *in-vivo* assessment of GRDDS. Per-oral endoscopy using a fiberoptic and video system is a component of gastroscopy.

DRAWBACKS

The drawbacks associated with different types of GRDDS are listed below.

Table 3: Drawbacks associated with different types of GRDDS.

Technology	Drawbacks
High density system	Quite challenging to incorporate a lot of medications. Such systems are not currently offered on the market.
Floating system	The ability to float heavily depends on how full the stomach is, and more fluid is needed in the gastric region.
Expandable system	Chocking issue, storage issue with hydrolyzable and biodegradable polymers, challenging manufacturing process, and unfeasible price
Mucoadhesive system	Due to the stomach's peristaltic wave and the quick turnover of mucus, might become separated from the gastric mucosa. It might also stick to the oesophageal mucous.
Magnetic system	Patient compliance issue

APPLICATIONS OF GRDDS

The limited absorption window in the upper section of the GIT makes it possible for medications with low bioavailability to be delivered in a number of ways using gastro retentive drug administration.

Sustained Drug Delivery

HBS systems can stay in the stomach for extended periods of time, allowing the medicine to release gradually. With these approaches, the issue of a brief gastric residence period that arises with an oral CR formulation can be resolved. These systems can float on the gastric contents since they have a bulk density of 1. Nicardipine hydrochloride sustained release floating capsules were compared to commercially available MICARD capsules using rabbits. In comparison to standard MICARD capsules (8 hours), sustained release floating capsules showed a longer duration for administration (16 hours) on plasma concentration time curves.

Site-Specific Drug Delivery

These systems are especially useful for medications like furosemide that are primarily absorbed from the stomach or the first part of the small intestine. According to reports, a monolithic floating dosage form with an extended stomach residence duration was created, increasing the bioavailability. The floating tablets AUC was around 1.8 times greater than that of regular furosemide tablets.

Absorption Enhancement

Potential possibilities for formulation as floating drug delivery systems include medications with low bioavailability due to site-specific absorption from the upper gastrointestinal tract, which would maximize their absorption. Comparing the bioavailability of floating dosage forms (42.9%) to currently available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%), a substantial improvement was seen.[23,24]

Treatment of diseases

Peptic Ulcer Disease

Drugs like proton pump inhibitors or H2 receptor antagonists can be administered through gastroretentive systems to treat peptic ulcers.

Gastroesophageal Reflux Disease (GERD)

Gastroretentive systems can be advantageous for medications used to treat GERD, such as antacids, proton pump inhibitors, and prokinetic drugs.[25]

Motion Sickness

Antiemetic medications can be administered using gastroretentive systems to treat motion sickness.

Diabetes

Drugs for the control of diabetes, such as oral hypoglycemic medications, can be delivered using gastroretentive systems.[26]

MARKETED PRODUCTS

Table 4: The marketed products are listed below.

Brand Name	Active Ingredients
AlmagateFlatCoat®	Ciprofloxacin
Cifran OD®	Aluminium-magnesium antacid
FlatCoat®	Aluminium-magnesium antacid
Madopar®	LDopa and Benserazide
Liquid Gavision®	Aluminium hydroxide
Cytotec®	Misoprostal
Valrelease®	Diazepam
Conviron®	Ferrous sulfate
Xifaxan®	Rifampicin
Baclofen GRS®	Baclofen
Accordion Pill®	Carbidopa/levodopa
Inon Ace Tables®	Simethicone
Glumetza	Metformin hydrochloride

CONCLUSION

According to the many approaches that have been developed in these delivery systems for the site-specific and disease-specific action of the molecules in these technologies using the many polymeric conditions that according to the site-specificity and their effectiveness, gastro retentive is the most advantageous approach for delivery of the specific quality and quantity of the drug for some long-term disease treatments. Many drug delivery systems are being developed nowadays with the goal of releasing the medication in the gastric region. Despite the fact that these medication delivery methods provide a number of benefits. They also have drawbacks, such as an extremely low *in-vitro in-vivo* correlation. The physiological processes that occur in the GIT must be taken into account, along with the proper medication and excipient combinations and formulation techniques. As a result, it is anticipated that numerous pharmaceutical corporations would start utilizing gastroretentive drug delivery technology in the future to produce fantastic benefits, lengthen patents, and improve the results for their marketed formulations.

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