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Gastro Retentive Drug Delivery System Current Chalenges and Future Perspective

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Abstract: A new method of administering medications is the use of gastro-retentive drug delivery systems (GRDDS). In order to ensure site-specific release in the upper gastrointestinal tract for both local and systemic effects, their main goal is to extend a drug's residence duration in the stomach. Regular dosing is necessary because some drugs that have been absorbed through the gastrointestinal tract (usually with short half-lives) are rapidly removed from the circulatory system. Because they are only absorbed in one location, immediate release oral administration systems are the most widely used to treat illness. Density, dosage form size, and shape are among the physicochemical characteristics of GRDDS that are crucial to its formulation. High-density systems sink to the bottom of the stomach, while dose forms with a density less than the contents of the stomach can float to the top. Because they have a lower bulk density than gastric fluids, floating drug delivery systems (FDDS) float in the stomach for extended periods of time without slowing down the rate of gastric emptying. The ability of novel adhesive materials made from synthetic or bacterial fimbrae to adhere to the gut has also been investigated. Nevertheless, the stomach wall's propulsive force is greater than the gastric mucoadhesive force. The constant creation of mucus and diluting of the stomach content are further drawbacks of this type of system. Several strategies, such as floating and non-floating systems, have been developed to enhance the retention of an oral dosage form in the stomach.

Keywords: *Gastro-Retentive Drug Delivery Systems, Anatomy and Physiology of the Stomach, Physicochemical Properties of GRDDs, Mechanism of Floating Drug Delivery System, Approaches to Fabricate Gastro-Retentive Systems,*

INTRODUCTION

A new method of administering medications is the use of gastro-retentive drug delivery systems (GRDDS). In order to ensure site-specific release in the upper gastrointestinal tract for both local and systemic effects, their main goal is to extend a drug's residence duration in the stomach. The prolonged stomach residence of formulations intended for gastro-retentive administration greatly increases their gastric retention time (GRT). Many methods for administering gastro-retentive medications have been developed in the last few decades. The most practicable and advised way to achieve systemic circulation of medicines is still oral administration [1]. A new method of administering medications is the use of gastro-retentive drug delivery systems (GRDDS). In order to ensure site-specific release in the upper gastrointestinal tract for both local and systemic effects, their main goal is to extend a drug's residence duration in the stomach. The prolonged stomach residence of formulations intended for gastro-retentive administration greatly increases their gastric retention time (GRT). Many methods for administering gastro-retentive medications have been developed in the last few decades. The most practicable and advised way to achieve systemic circulation of medicines is still oral administration [2]. Ranitidine and metformin, for example, are labile at alkaline pH [3], furosemide and diazepam are poorly soluble at alkaline pH [4], and levodopa and riboflavin have a limited window of absorption [5].

Improved patient compliance by lowering the frequency of dosing; enhanced therapeutic efficacy of medications with short half-lives; site-specific delivery of medications; sustained and controlled release of drugs in the stomach; increased residence time of drugs at the absorption site; improved bioavailability from the gastrointestinal tract; and preventing dose dumping of medications are some of the common benefits associated with the use of GRDDS [6]. These delivery systems

are designed to stay in the stomach following oral administration, releasing the medication in a regulated way that supplies the gastrointestinal tract (GIT) absorption sites continuously. However, irregular gastric emptying time (GET) and short GRT pose problems since they can result in decreased dose efficacy and partial drug release in the absorption zone (the stomach or upper small intestine) [7]. Furthermore, peptic ulcer therapy and other local treatments in the upper small intestine may benefit from prolonged gastric retention [8]. Ion-exchange resins, high-density materials, raft-forming materials, magnetic compounds, and super porous hydrogels are among the materials used to create GRDDS [9,10].

Table: 1. Gastro Retentive Drug Delivery Systems Vs Conventional Drug Delivery Systems [11].

Sr. No.	Parameters	Conventional DDS	Gastro Retentive DDS
1.	Toxicity	High risk of toxicity	Low risk of toxicity
2.	Patient compliance	Less	Improve patient compliance
3.	Drug with narrow absorption window in small intestine	Not suitable	Suitable
4.	Drug having rapid absorption through GIT	Not much advantageous	Very much advantageous
5.	Drug which degrades in the colon	Not much advantageous	Very much advantageous
6.	Drug act as locally in the stomach	Not much advantageous	Very much advantageous
7.	Drug which are poorly soluble act an alkaline pH	Not much advantageous	Very much advantageous
8.	Dose dumping	High risk of dose dumping	No risk of dose dumping

NEED OF GRDDS

Regular dosing is necessary because some drugs that have been absorbed through the gastrointestinal tract (usually with short half-lives) are rapidly removed from the circulatory system. Gastro-retentive drug delivery devices are an innovative solution to this problem. Their high plasma drug concentration lowers the frequency of doses. By administering the medication in a controlled and uniform manner, this strategy also removes fluctuations in plasma drug concentration [12].

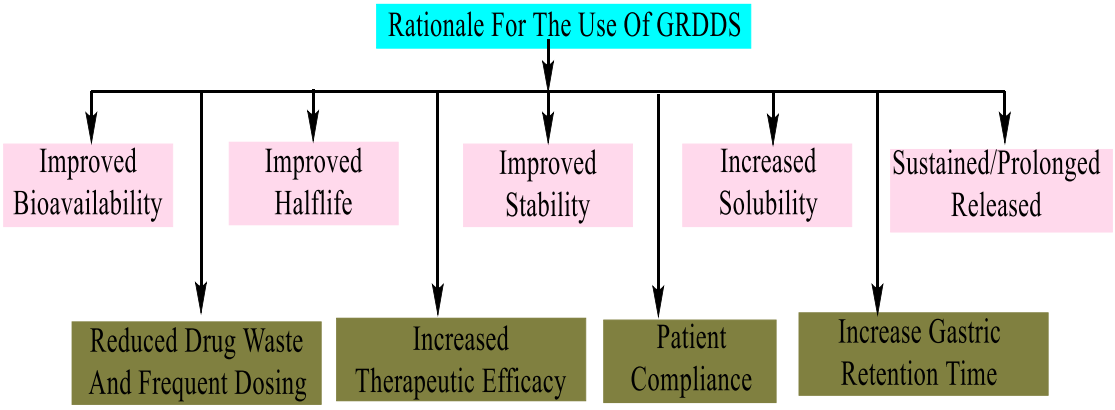


Figure: 1. The Rationale for the Use of GRDDS [13].

Importance of GRDDS in the Field of Pharmaceutics

Because they are only absorbed in one location, immediate release oral administration systems are the most widely used to treat illness. The development of gastro-retentive drug delivery techniques is required due to the shortcomings of the instant release dosage form. These devices will help keep medications at particular locations for longer. This is achieved by maintaining the dosage form in the stomach and releasing the medication in a controlled manner at specific sites in the intestine, duodenum, and stomach [14].

Anatomy and Physiology of the Stomach

The successful creation of gastroretentive dosage forms requires an understanding of the anatomy and physiology of the stomach. The stomach is separated anatomically into three sections: the fundus, which is located closest to the esophagus; the body, which stores food that has been swallowed; and the antrum, which is the final section that joins the body to the small intestine. Antrum aids in stomach emptying and churning [15]. Every 120 to 180 minutes during a fast, the stomach and intestine undergo a series of contractions known as the migrating myoelectric cycle. It is further separated into four stages. The term "digestive motility pattern" refers to the pattern of contraction changes in a fed state [16]. The movement

of the GIT, or the emptying of the gastric tract and the intestinal transit, is caused by the several layers of smooth muscles. There are three sections to the stomach.

1. Fundus
2. Body
3. Antrum Pylorus [11].

The antrum is the primary location for mixing motions and functions as a stomach pump through pushing action, whereas the proximal part, which is made up of the fundus and the body, serves as a storage area for unmined material. Both fed and fasted conditions result in gastric emptying [17, 18]. The migratory patterns in the two states, however, differ. Every two to three hours, an electrical event takes place between the intestines during a fast. There are four phases to this cycle, which is known as the migration myloelectric cycle (MMC) or interdigestive myloelectric cycle [19].

1. **Phase I (Basal phase):** lasts 30-60 minutes without contraction.
2. **Phase II (Pre-burst phase):** last for 20-40 minutes with intermittent action potential and contraction. With the progression of the phase, the intensity and frequency also increase gradually.
3. **Phase III (Burst Phase):** This phase lasts between 10 and 20 minutes and includes short-term intense and regular contractions.
4. **Phase IV:** Phase III to Phase I transition period: 0 to 5 minutes [11]. The contraction pattern shifts from the fast state to the feeding state following a mixed meal. It features constant contractions similar to phase 2 of the fasting condition and is also referred to as the digestive motility pattern [20].

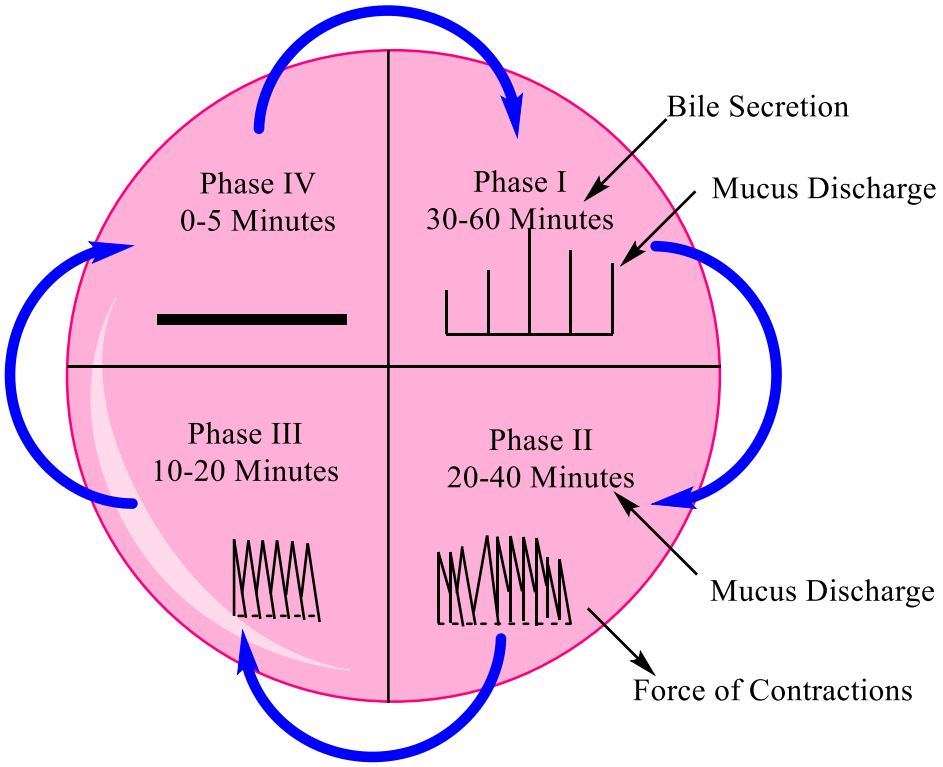


Figure: 2. Phases of Gastric Motility and Gastric Emptying Rate [11].

Stomach Functionalities

1. The stomach performs the following functions [21].
2. Temporary storage to allow digestive enzymes, pepsins to act
3. Pepsins are enzymes that break proteins down into polypeptides
4. Water, alcohol, and several lipid-soluble medications are examples of substances that limit absorption.
5. Non-specific microbial defence supplied by hydrolytic acid in gastric juice. Vomiting can occur as a result of ingesting stomach irritants such as bacteria or chemicals [22].

PHYSICOCHEMICAL PROPERTIES OF GRDDS

Density, dosage form size, and shape are among the physicochemical characteristics of GRDDS that are crucial to its formulation. High-density systems sink to the bottom of the stomach, while dose forms with a density less than the contents of the stomach can float to the top. The density should be between 1.0 and 2.5 g/cm3 for a perfect formulation. Better stomach residence time (GRT) is demonstrated by dosage forms with a diameter greater than 7.5 mm [23].

Physiological Factors Affecting Retention of GRDDS in the Stomach

The nature of the meal, caloric amount, frequency of feeding, and fed or unfed condition are the most significant factors influencing the stomach retention duration of dose forms. Gastric retention duration is reduced in a fasting condition because GI motility is increased. Peristalsis causes the stomach's contents to empty. The stomach residence is brief if peristalsis and dose form delivery occur at the same time. Gastric retention time is increased by a high-calorie meal that contains fibrous materials, proteins, and lipids. Because peristalsis is continuously inhibited, there is increased stomach retention when there are several meals. Gastric retention is also influenced by a few other characteristics, including age and sex. Regardless of height, weight, or body surface, females have a slower stomach emptying time than males. An individual over 70 years of age has a longer GRT. Compared to elderly individuals, neonates exhibit lower GRT [24, 25, 26].

Classification of GRDDS

The two primary categories of GRDDS are floating and non-floating systems. Based on the method of floating, floating systems are further divided into effervescent and non-effervescent systems, whilst non-floating systems are divided into four groups according to the gastro retention mechanism [27].

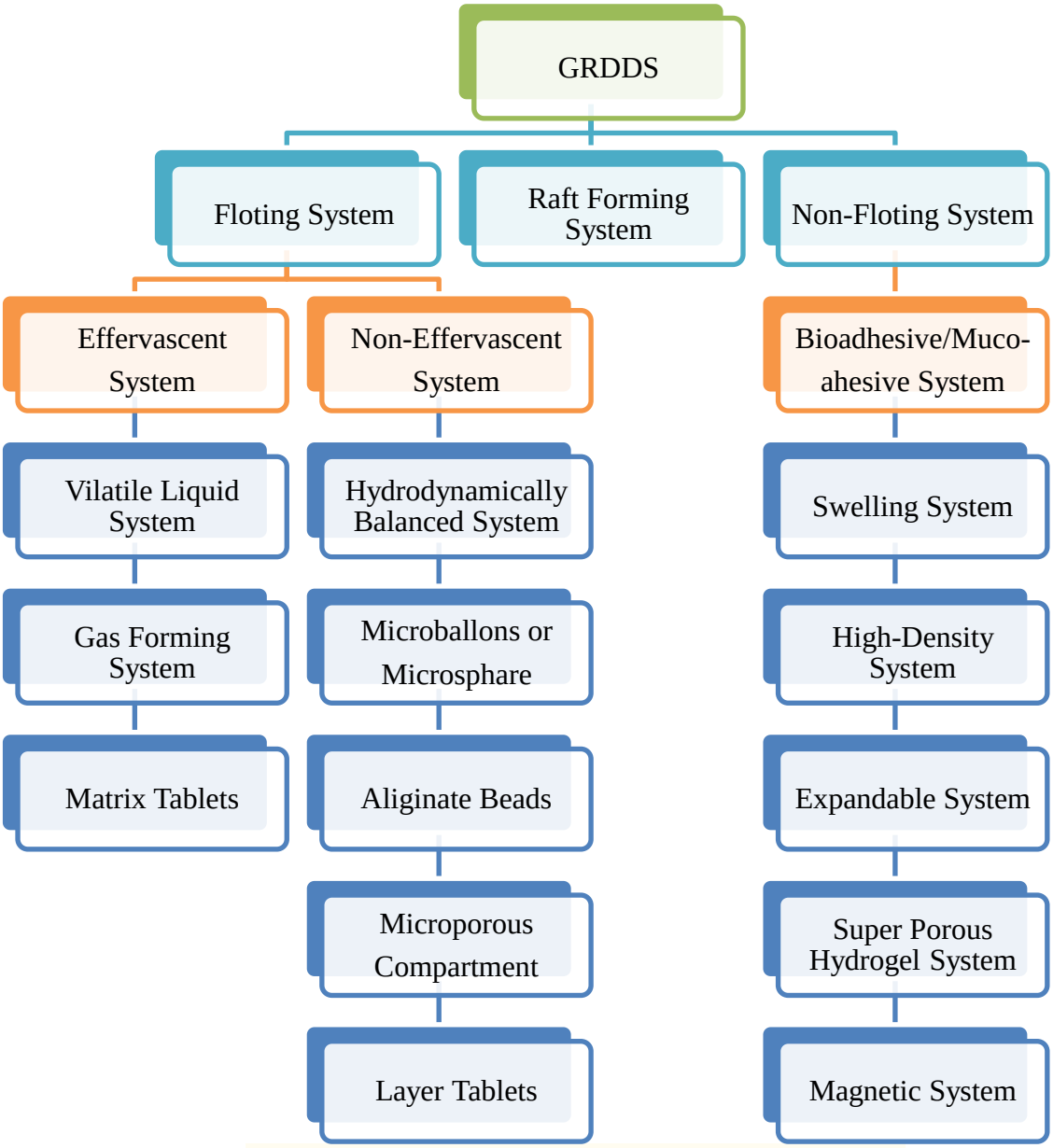


Figure: 3. Classification of Gastro-Retentive Drug Delivery System [28].

Floating GRDDS

Floating systems, which have a lower bulk density than the stomach content, were first described by Davis in 1968. They can release the drug continuously and remain hydrated in the stomach for long stretches of time. Finally, the remaining system is vacuumed. The stomach empties much more quickly during fasting, and floating systems mostly depend on food to delay emptying and provide enough fluid to keep them going. FDDS remain buoyant in the stomach for a longer period of time without slowing down the rate at which the stomach empties because they have a lower bulk density than gastric fluids. There are known delivery systems that swell to the point that they are unable to pass through the pylorus. Because the polymer absorbs water and expands when it comes into contact with gastric juice, the administered dose remains in the stomach for a longer period of time. Higher GRT and better control over changes in the plasma drug concentration could result from this. The two components of the floating drug delivery system are Raft forming and effervescent, non-effervescent systems [29].

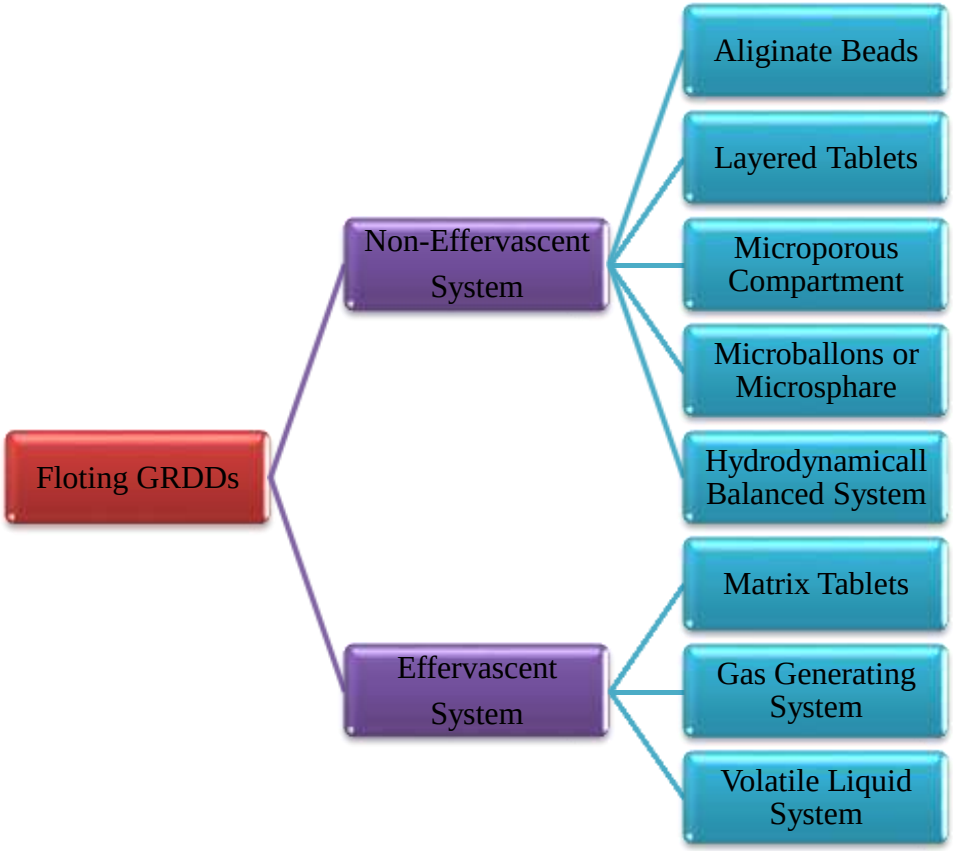


Figure: 4. Classification of Floating GRDDs [28].

Mechanism of Floating Drug Delivery System (FDDS)

Because they have a lower bulk density than gastric fluids, floating drug delivery systems (FDDS) float in the stomach for extended periods of time without slowing down the rate of gastric emptying. The drug is progressively released from the body at the necessary rate while the system is floating on the stomach's contents, as shown in Figure 5(a). However, in addition to the minimal stomach content required to accomplish the buoyancy retention principle, a minimal amount of floating force (F) is also required to keep the dose form continuously buoyant on the meal's surface. In order to assess the dynamics of the floating force, a particular method for computing resultant weight has been established in the literature.

In order to keep the submerged object underwater, the apparatus continuously measures the force equivalent to F (as a function of time). As shown in Figure 5, the object floats better if F is on the positive side. By preventing the detrimental consequences of unforeseen intragastric buoyancy capacity changes, this equipment serves to optimize FDDS in terms of the stability and longevity of the generated floating forces [30].

F = F buoyancy – F gravity = (Df – Ds) gv

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

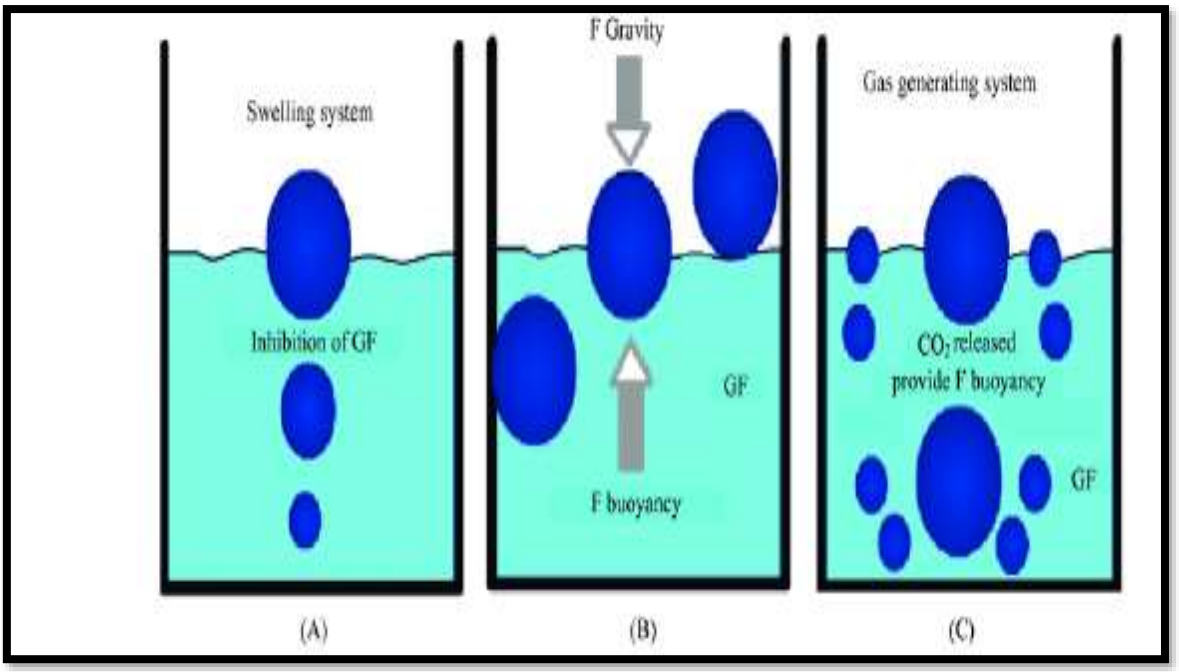


Figure: 5. Mechanism of Floating Drug Delivery System [31].

Non-Floating Drug Delivery Systems

1. High Density (Sinking) Drug Delivery System

The density of the formulation is higher than that of typical stomach contents. Density is increased to 1.5–2.4 gm/cm³ by the materials. Depending on density, pellets' GI transit time can be increased from 5.8 to 24 hours. Nevertheless, no formulation has been commercialized, and the effectiveness of this approach in humans has not been proven [32].

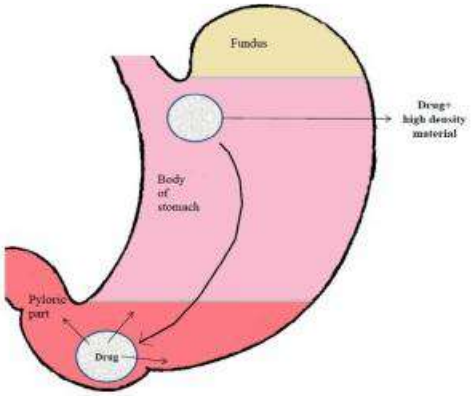


Figure: 6. High Density Drug Delivery System [33].

2. Bioadhesive or Mucoadhesive Drug Delivery System

By using the bioadhesive technology for the gastric mucous membrane, the gastric retention period has been prolonged. Bioavailability is increased by the delivery system's adherence to the stomach wall, which extends residence time. Gliadin, carbopol, lecithin, chitosan, polycarbophil, and carboxymethyl cellulose are among the substances utilized for mucoadhesion [34]. The ability of novel adhesive materials made from synthetic or bacterial fimbrae to adhere to the gut has also been investigated. Nevertheless, the stomach wall's propulsive force is greater than the gastric mucoadhesive force. The constant creation of mucus and diluting of the stomach material is another drawback of this type of system [33].

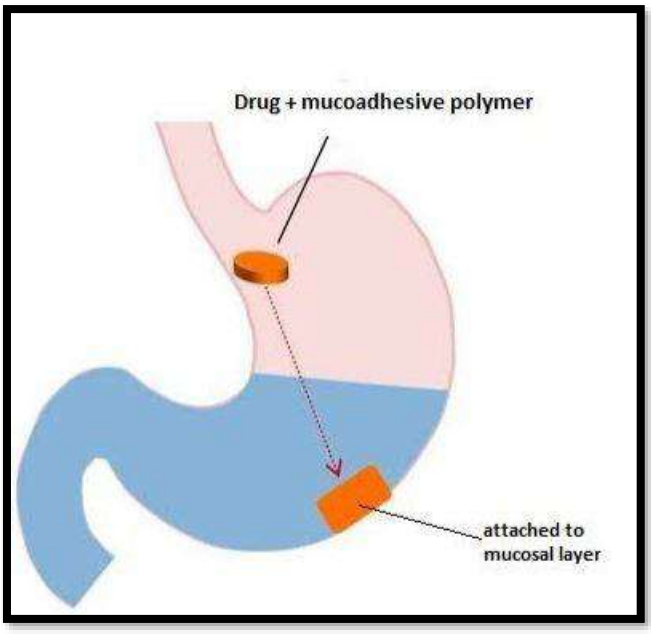


Figure: 7. Bioadhesive or Mucoadhesive Drug Delivery System [33].

3. Magnetic System

In this procedure, a small magnet is incorporated into the dosage form, and another magnet is positioned on the abdomen above the stomach. Precise setting of the external magnet may decrease patient compliance [33].

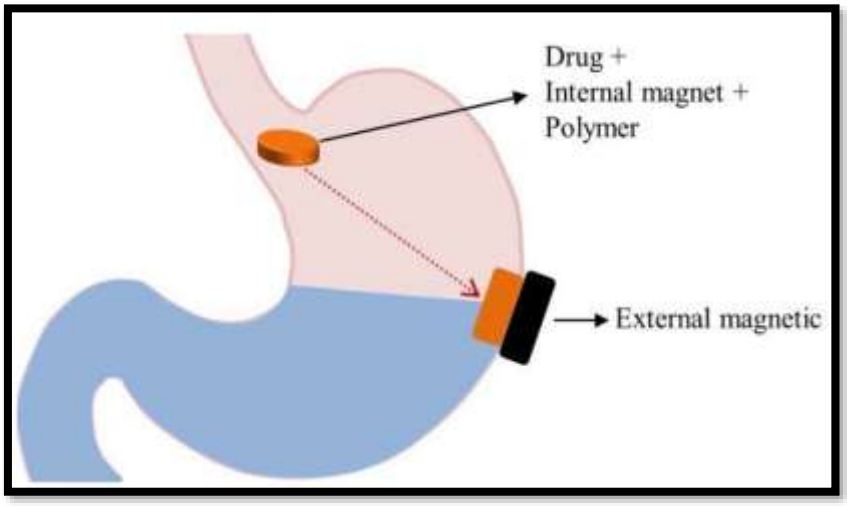


Figure: 8. Magnetic System [33].

4. Expandable System

These systems can expand and remain in the stomach for extended periods of time. These are often offered in capsules with a compressed and folded dosage shape. In the stomach environment, the capsule shell disintegrates and the dosage form swells, preventing it from passing through. By using the appropriate polymer, drug distribution can be controlled and sustained [33].

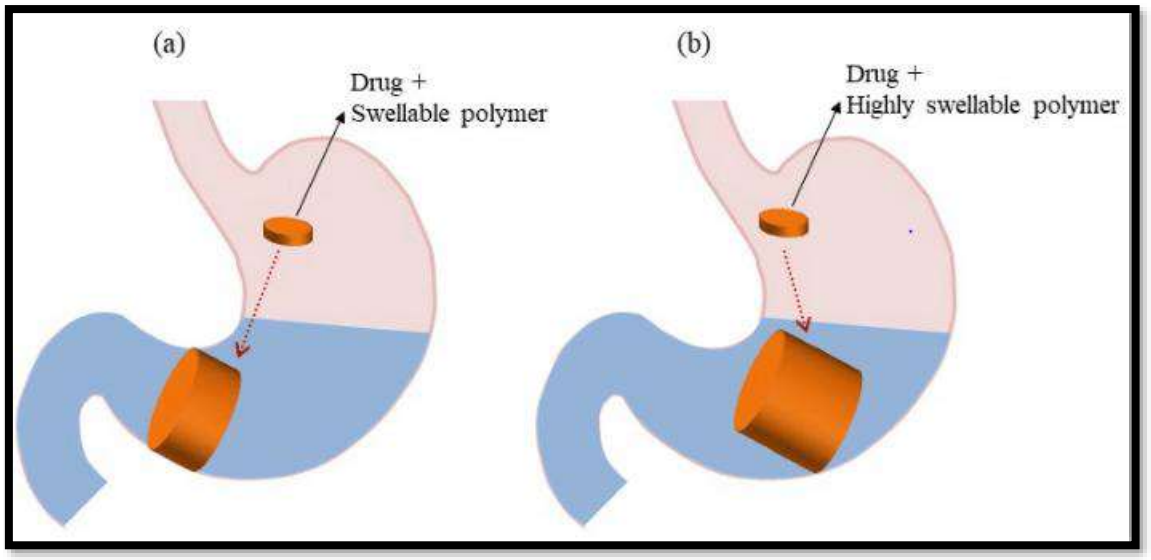


Figure: 9. Expandable System.

5. Raft Forming Systems

These systems use effervescent excipients and gel-forming polymers to provide sustained medication delivery. These devices are effective in producing a localized effect because they operate as a barrier between the stomach and the esophagus. Thus, gastric reflux disease and peptic ulcers can be treated using the device. A continuous layer known as a raft form when these systems come into contact with stomach fluid because they swell and form a viscous cohesive gel [35, 36]. Another new technique is the antacid raft forming method, which uses acid neutralizer, sodium bicarbonate, and sodium alginate as gas-generating agents and gel-forming polymers. Because CO2 production lowers the bulk density of the system, the raft floats on the stomach fluid. The medication can be constantly released while the raft floats on the stomach fluid for several hours. For the delivery of antacid drugs, these rafts are especially helpful [37]. These systems are subject to MMC due to their low mechanical strength [37, 38].

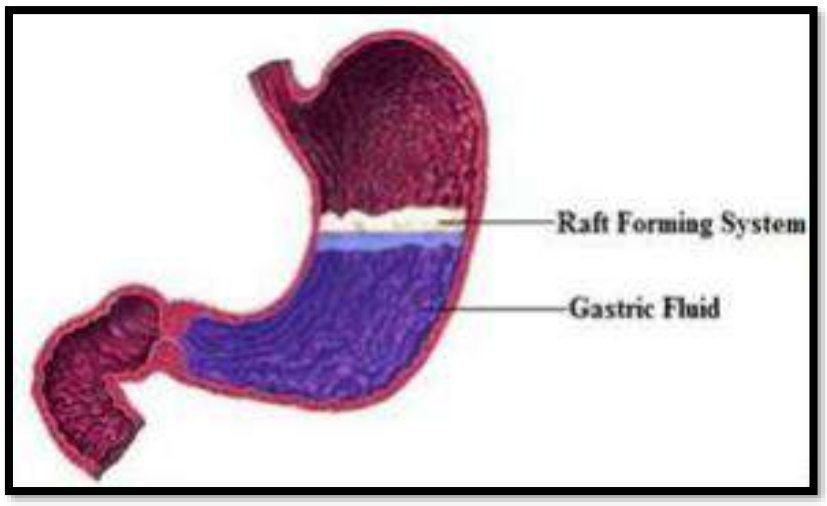


Figure: 10. Classification of Floating System

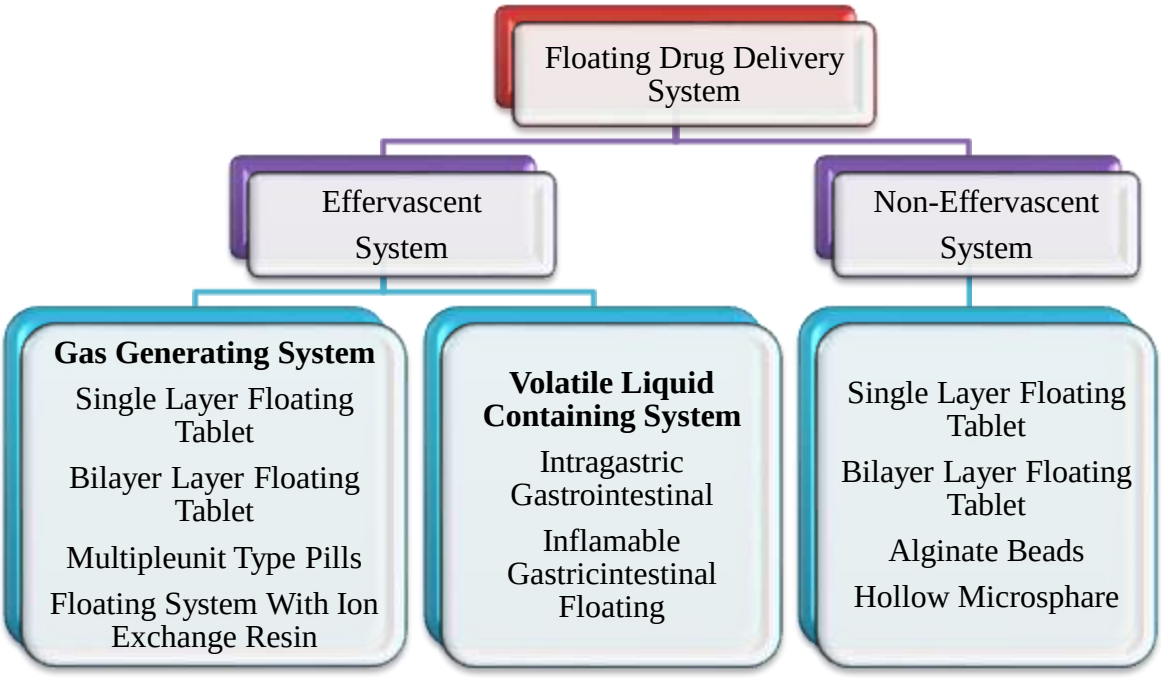


Figure: 11. Classification of Floating System [39].

Approaches to Fabricate Gastro-Retentive Systems

Researchers have used a variety of strategies to extend the duration of the drug's stomach residency. One such strategy is the high-density formulation concept, in which the created dosage form was made heavy (density: 2.5 to 3.0 g/ml) to survive in vivo peristaltic movement and stayed intact despite the GIT disturbance. Because the developed dosage form was made heavy (density: 2.5 to 3.0 g/ml), it was anticipated that the GI transit time would increase. In order to endure in vivo peristaltic movement and maintain its integrity despite the GIT disturbance, the produced dosage form was designed heavy (density: 2.5 to 3.0 g/ml). As a result, it was anticipated that the GI transit time would increase by an average of 5.8 to 25 hours [40,41]. To make the dosage form denser, iron powder, zinc oxide, titanium oxide, and barium sulfate were added. According to Chawla et al. [42], one of the main disadvantages of this type of technology was the increased dose size needed to attain that high density. Using a magnetic field to keep the dosage form in the stomach was another innovative concept. Magnetically active components would be present in the dose form. To keep the given medication in place, one external magnet had to be placed on the abdomen over the stomach. Despite its revolutionary design, one of the main obstacles to the in vivo design of this delivery system was patient noncompliance [43].

APPROACHES FOR GASTRO RETENTION

Several strategies, such as floating and non-floating systems, have been developed to enhance the retention of an oral dosage form in the stomach. Effervescent and non-effervescent systems are examples of floating systems; they have a bulk density that is lower than that of stomach fluid, stay afloat, and release the medication gradually at the prescribed rate. Bioadhesive, swelling, high density, expandable, raft-forming, and magnetic systems are examples of non-floating devices that use various processes to stop medications from passing through pyloric sphincters [44].

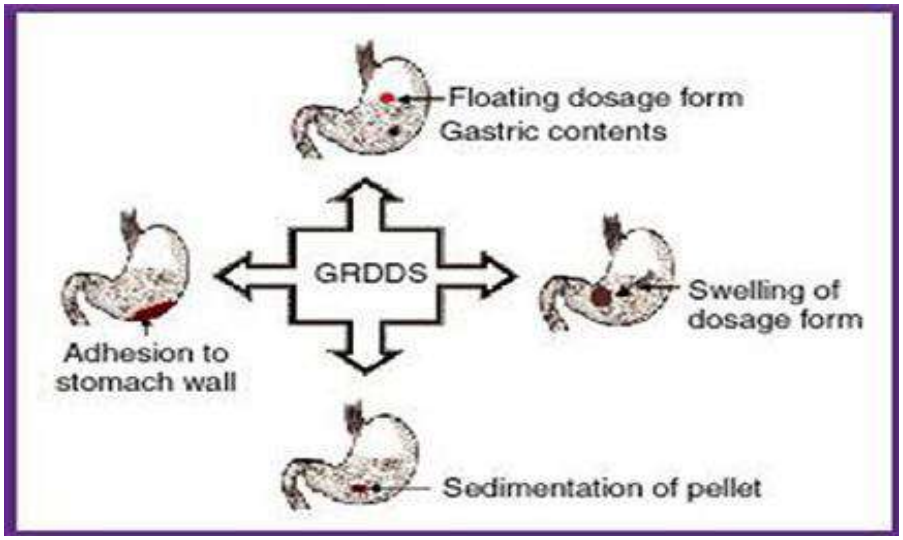


Figure: 12. Approaches for Gastro Retention [45].

Floating Capacities of SGL-HPMC *sf* GRDDS Tablets.

Floating Capacities	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
FLT [1] (s)	4± 1	3± 1	2± 1	2± 1	2± 1	2± 1	2± 1	2± 1	2± 1	2± 1	2± 1	2± 1
TLT [2] (h)	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24
[1]FLT= Floating lag time; [2]TFT= Total floating time. Data represent mean ± standard error of the mean (n=3 for each group).												

Table: 2. Floating Capacities of SGL-HPMC *sf* GRDDS Tablets [46].

1. Effervescent System

Floating of a medication delivery device in an inert gas, air, or vacuum-filled stomach. The volatilization of an organic solvent (such as ether or cyclopentane) or the CO2 generated via an effervescent reaction between organic acids and carbonate-bicarbonate salts can both bring gas into the floating chamber. In order to allow the spontaneous ejection of a thin floatable system from the stomach, these devices have a hollow deformable unit that changes from a collapsed to an expanded state and returns to the collapsed position after a predefined period of time [47].

a) Volatile Liquid Containing Systems

An impermeable, pressure-responsive, moveable bladder divides the two chambers in this kind of system. The medicine is kept in the first chamber, while the volatile liquid is kept in the second. By adding an inflatable chamber that holds a liquid, such as ether or cyclopentane, that gasifies at body temperature to cause the chamber in the stomach to inflate, the GRT of a drug delivery system can be maintained. In order to allow the inflatable systems to spontaneously exit the stomach, the device may also include a bioerodible plug composed of poly vinyl alcohol, polyethylene, etc. that progressively dissolves, allowing the inflated chamber to release gas and collapse after a set amount of time. The medication is constantly discharged from the reservoir into the stomach fluid as the device expands [48].

b) Gas Generating System

The creation of gas bubbles is another way to attain floatability. By adding carbonates or bicarbonates, which react with acid—either naturally occurring stomach acid or co-formulated as citric or tartaric acid—CO2 can be produced in situ. According to reports, the ideal stoichiometric ratio of sodium bicarbonate to citric acid for gas production is 0.76:1. Another option is to use a matrix that contains trapped liquids, which at body temperature turns into a gas. These methods have been used to systems with one or more units.

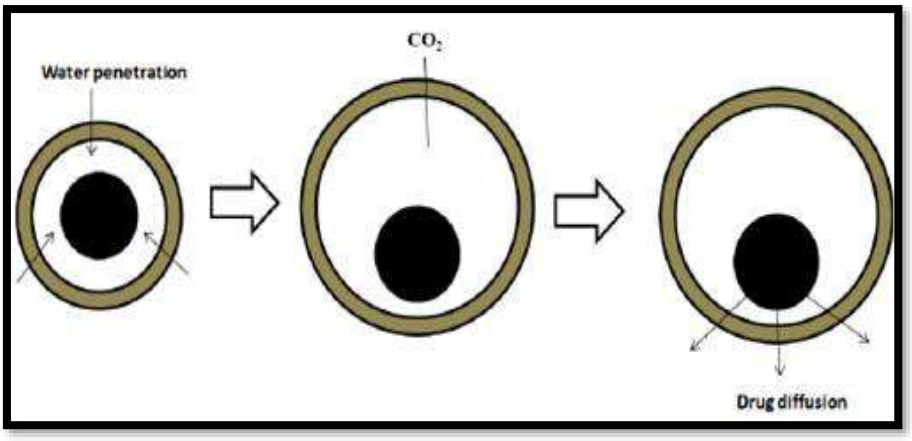


Figure: 13. Gas Generating System [49].

2. Non-Effervescent Systems

Include in tablets or capsules a high concentration (20–75% w/w) of one or more gel-forming, highly swellable cellulosic hydrocolloids (such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (HPMC), and sodium carboxymethyl cellulose), polysaccharides, or matrix-forming polymers (such as polycarbophil, polyacrylates, and polystyrene) [50]. The mechanism of polymer swelling or bioadhesion to the GI tract's mucosal layer provides the basis for non-effervescent FDDS. Gel-forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides, matrix-forming materials like polycarbonate, polyacrylate, polymethacrylate, and polystyrene, as well as bioadhesive polymers like chitosan, are the most often utilized excipients in non-effervescent FDDS [51,52].

a) Single Layer Floating Tablets

They are made by carefully combining the medication with a gel-forming hydrocolloid that expands when it comes into contact with stomach fluid and keeps its bulk density below unity. These dose forms are buoyant due to the air retained by the inflated polymer [39].

b) Bilayer Floating Tablets

A bilayer tablet has two layers: an immediate release layer that releases the first dose from the system, and a sustained release layer that absorbs gastric fluid and forms an impermeable colloidal gel barrier on its surface. The sustained release layer maintains a bulk density of less than unity, which keeps the tablet buoyant in the stomach [39].

c) Alginate Beads

Freeze-dried calcium alginate has been used to create multi-unit floating dosage forms. By adding sodium alginate solution to an aqueous calcium chloride solution, calcium alginate will precipitate, creating spherical beads with a diameter of around 2.5 mm. A porous system that can sustain a floating force for more than 12 hours is created after the beads are separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours. A longer residence time of over 5.5 hours was provided by these floating beads [53].

d) Hollow Microspheres (Microballoons)

A novel emulsion solvent diffusion method was used to create hollow microspheres loaded with medicine in their outer polymer shelf. The drug's ethanol/dichloromethane solution and an enteric acrylic polymer were added to an agitated Poly Vinyl Alcohol (PVA) solution that was thermally regulated at 40ºC. The internal cavity in the microsphere of the drug-containing polymer and the evaporation of dichloromethane create the gas phase in the dispersed polymer droplet. For nearly 12 hours, the microballoon continued to float across the surface of an acidic dissolving medium that contained surfactant [54,55].

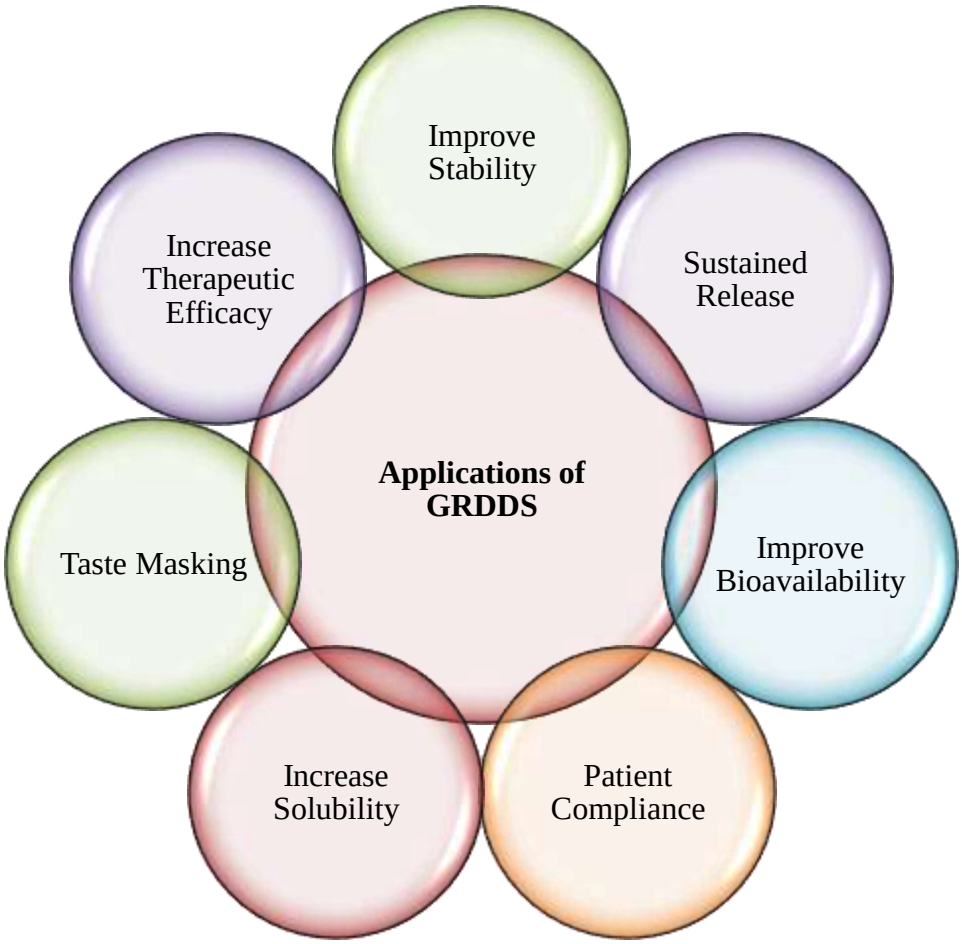


Figure: 14. Application of GRDDS [28].

Swallable System or Extandable System

These are the dose forms that expand so much after eating that they are unable to pass through the pylorus. As a result, the dose is held in the stomach for a longer amount of time. Because these systems typically stay recorded in the Pylori sphincter if the expansion diameter is more than 12–18 mm, they may be referred to as plug-type systems. The extent and duration of the swell are maintained by the equilibrium between the degree of cross link between polymer chains. The system's ability to grow and sustain its physical integrity over an extended length of time is accelerated by a high cross-link [56,57].

Super Porous Hydrogel System

Swelling distinguishes these from traditional systems. Conventional hydrogels absorb water relatively slowly, taking several hours to attain equilibrium and removing the dose form too soon [58]. Superporous hydrogels, which have a diameter of more than 100 micrometers, quickly consume water through open holes connected by capillary rain, causing them to expand to equilibrium in a matter of minutes. They have enough mechanical resistance to endure the pressure of a stomach contraction and expand to a bigger size. Ac Di-Sol, a hydrophilic particle, is co-financed to do this [59].

Magnetic System

A tiny internal magnet is applied to the abdomen and positioned over the stomach as part of the dose form. Extracellular magnets can be used to prolong the dose form's gastric life time [60,61].

Challenges Ahead With GRDDS

One factor influencing the bioavailability of oral drug delivery systems is the duration of the dosage forms' retention in the gastrointestinal tract. When it comes to GRDDS, the stomach is the sole organ affected. Therefore, keeping the delivery system in the stomach or upper portion of the small intestine for an extended period of time until all of the medications have been given at a predefined pace is the primary difficulty for designing a GRDDS [62]. The fasting condition shortens

the stomach retention period, while the fed state lengthens it [63]. The difference in gastric emptying time is mostly influenced by other physiological barriers and factors such as food type, caloric content, gender, and age [64].

Furthermore, according to Mojaverian et al. [65], patients' GRT varies based on their age and gender. Additionally, indigestible polymers or fatty acid salts alter the stomach's motility pattern when it is fed and aid in lowering the pace of gastric emptying [66]. Any GRDDS's gastric retention is significantly influenced by the pylorus limitation. During digestion, the pylorus is roughly 2 to 3 mm in size, and during the inter-digestive phase, its diameter increases to 12.8 ± 7.0 mm [67]. The difference between the pylorus size and peristaltic movement of an animal (such as a dog or rabbit model) and that of a person should also be taken into account [68].

In contrast to a single-unit GRDDS, multiple-unit GRDDS has occasionally been shown to exhibit better and more consistent drug release. A single unit gastro-retentive dosage form (GRDF) may eventually leave the stomach before the dosage form becomes functional due to a combination of the lag period and the gastric emptying process [69]. Therefore, overcoming issues related to the stomach's gastric emptying rate and sustaining a suitable drug release rate for a long time before it is metabolized in the system are the primary hurdles in developing an ideal GRDDS [70].

FUTURE PERSPECTIVES OF GRDDS

One of the biggest issues facing the pharmaceutical business is the GRT of the standard dose form, particularly for medications that are absorbed from the upper region of the intestine. Although more research is required to address its flaws, developing GRDDS will aid in overcoming the disadvantages of current dosage forms. The single system technique has been used in numerous GRDDS investigations to far, including expandable, mucoadhesive, and floating systems. The variance in GRT, particularly in the fed and fasted stages, remains one of the primary issues faced by many formulation scientists, despite the fact that numerous GRDDS technologies have been thoroughly investigated to produce successful gastroretentive systems. There may be no one strategy that works best to solve the issues. Investigating appropriate GRDDS that can get around the drawbacks of a single strategy is therefore desirable. Combination techniques including expandable and effervescent floating systems, mucoadhesive and floating systems, swellable and floating systems, and mucoadhesive and high-density systems could be effective ways to reduce GRT variability. Furthermore, dual-working systems can guaranty delayed gastric emptying and are less impacted by the physiological conditions of the stomach, such as the fed and fasting stages. In order to extend the stomach retention of dose forms even while fasting, future research on GRDDS should concentrate on combining several processes [71].

Because product specifications may affect the physiochemical nature of the medication and excipients, kinds and composition of polymers, drug dose, and manufacturability, it is crucial to evaluate gastroretentive dosage forms on a case-by-case basis [72].

Understanding how formulation and process variables affect GRDDS's critical quality features is another crucial component of enhancing GRDDS. Floating behavior, floating force, gel strength, mucoadhesive strength, mucoadhesive time, in vitro drug release, swelling capacity, hydrogel porosity, tablet tensile strength, and friability are among the essential qualities of GRDDS. From a formulation perspective, the logical construction of the gastroretentive dosage form depends on an understanding of polymer behavior and its role in formulation. Additionally, choosing the right polymer concentration is crucial for creating these dosage forms. In this sense, the quality by design (QbD) method can be a helpful tool for examining how formulation and process variables affect the important GRDDS quality features. The understanding and management of the production process have significantly changed as a result of the application of the QbD approach in the pharmaceutical industry, which significantly reduces the risk of product failure [73].

Certain gastroretentive techniques, including magnetic systems, have not been thoroughly investigated. These systems' clinical research has not yet been thoroughly documented. Future research on magnetic systems must therefore concentrate on clinical candidates in order to define their useful uses in people. Furthermore, because the superporous hydrogel system expands and takes up more space, adding magnetic systems can aid extracorporeal magnets in accurately locating the ingested dosage form. Technological advancements have made it possible to predict and link the passage of drugs into the GIT and the time it takes for the stomach to empty. For instance, gastric emptying of dose forms from the stomach can be assessed in vivo using radiography and scintigraphy [74]. Additionally, dose forms in the stomach can be photographed using magnetic marker monitoring techniques [75].

Advantages of Gastro-Retentive Drug Delivery System

1. It increases patient compliance by reducing dosing frequency.
2. Buoyancy increases gastric residence time.
3. Better therapeutic effect of short half-life drugs.

4. Site specific drug delivery to stomach can be achieved.
5. Gastric irritation can be avoided by designing sustained release.
6. No risk of dose dumping by making single unit floating unit such as microspheres releases drug uniformly [76,77].
7. Targeted therapy for local ailments in the upper GI tract [78].

Disadvantages of Gastro-Retentive Drug Delivery System

1. One drawback of floating systems is that they need a lot of fluid in the stomach to stay afloat and function well. Therefore, with this dosage form, drinking additional water is advised.
2. When in a supine position, such as when sleeping, floating dose forms may be carried away by contractile waves if they are not larger. Therefore, the patient shouldn't take the floating dose form right before bed.
3. Drugs that irritate the stomach mucosa, have stability issues in highly acidic environments, or have extremely low solubility in acidic environments cannot be included in GRDDS.
4. Bio/mucoadhesive systems have issues with thick mucus layers, high mucus layer turnover rates, and restrictions relating to soluble mucus [79].

CONCLUSION

Drugs having limited absorption windows, high solubility at acidic pH, and instability at alkaline pH may benefit greatly from GRDDS. The successful design of GRDDS requires a detailed understanding of the stomach's anatomy and physiological state, as well as research into how formulation and process variables affect dosage form quality. Although a number of GRDDS, including bio/mucoadhesive, magnetic, low-, and high-density systems, have been documented in the literature, further research is necessary to determine their therapeutic importance. Future GRDDS approaches may need to concentrate on a combined strategy in order to improve product quality from a pharmacological perspective. Furthermore, a QbD approach can be utilized to gain a deeper understanding of how formulation and process variables affect product performance. A new method of administering medications is the use of gastro-retentive drug delivery systems (GRDDS). In order to ensure site-specific release in the upper gastrointestinal tract for both local and systemic effects, their main goal is to extend a drug's residence duration in the stomach.

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