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THE FUTURE PERSPECTIVES AND NOVEL APPROACH ON GASTRO RETENTIVE DRUG DELIVERY SYSTEM (GRDDS) WITH CURRRENT STATE

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Abstract:
Gastroretentive drug delivery systems (GRDDs) are designed to prolong the residence time of a drug in the stomach. This can be beneficial for drugs that are destroyed by stomach acid or that need to be delivered in a sustained-release manner. GRDDs are a promising new technology for improving the delivery of drugs to the gastrointestinal tract. They have the potential to improve the efficacy and safety of drugs, and to reduce the number of side effects. The primary goal of GRDDs is to improve the bioavailability and therapeutic efficacy of orally administered drugs. GRDDs are available in GRDDs can take various forms, including tablets, capsules, or multiparticulate systems. They are formulated using various strategies to achieve gastroretention, such as floating systems, mucoadhesive systems or expandable systems & swelling. The primary focuses of this review paper are to first go through the fundamental idea of GRDDs, the most recent approach to GRDDs, and the situation of GRDDs delivery today. In this review, talk about the stomach's physiological condition and the many components that influence GRDDS. Recently used gastrointestinal technologies such as expandable, bio/mucoadhesive, low- and high-density-systems, and adhesive have also been briefly studied, along with their benefits and drawbacks.

Keywords: Gastro retentive drug delivery system (GRDDs); CR; Conventional Drug Dosage Form; Bioavailability; Gastric Retention Time.

INTRODUCTION

Oral drug delivery systems have dominated other drug delivery systems for human administration due to their various advantages including ease of administration, flexibility in formulation, cost-effectiveness, easy storage and transport, and high patient compliance. Oral drug delivery systems face challenges such as low bioavailability due to the heterogeneity of the gastrointestinal system, pH of the commensal flora, gastric retention time of the dosage form, surface area, and enzymatic activity. GRDDs are a type of drug delivery system that is designed to prolong the residence time of a drug in the stomach [1]. This can be beneficial for drugs that are poorly absorbed in the small intestine, sensitive to stomach acid, or need to be delivered to the stomach.

A system where gastric retention time coupled with the drug release for extended time has improved patients compliance. GRDDs can remain in gastric region for several hour and prolong the gastric residence time of drugs. Prolonging the gastric retention time with improve solubility, bioavailability and reduce the drug waste.

GRDDs is an approach to prolong the GRT, targeting drug release in upper GIT for local and systemic effect. GRDDs can boost controlled delivery of drug with absorption window by releasing the drug for extended period of time before reached absorption site. The objective of a gastroretentive drug delivery system (GRDDs) is to prolong the residence time of a drug in the stomach [1-2]. This can be achieved by using a variety of techniques, such as:

- ***Floating systems:*** These systems are made of materials that are less dense than gastric fluid, so they float on top of the fluid and are not easily emptied by peristalsis.
- ***Mucoadhesive systems:*** These systems adhere to the lining of the stomach, making it more difficult for them to be moved by peristalsis.
- ***Magnetic systems:*** These systems contain magnetic particles that can be manipulated by an external magnetic field. This can be used to keep the system in a specific location in the stomach.
- ***Expandable systems:*** These systems expand in the stomach, making it more difficult for them to be emptied [1-3].

GRDDs are used for a variety of drugs, including:

- Drugs that are absorbed from the stomach (e.g., omeprazole, lansoprazole).
- Drugs that are labile at alkaline pH (e.g., ranitidine, metformin).
- Drugs that are poorly soluble at alkaline pH (e.g., furosemide, diazepam).
- Drugs that have a narrow window of absorption (e.g., riboflavin, levodopa).

GRDDs are feasible for drugs that have low absorption in the lower part of the GIT, are unstable and poorly soluble at alkaline pH, have a short half-life, and show local activity at the upper part of the intestine for eradication of Helicobacter pylori GRDDs are a promising technology for improving the delivery of drugs to the stomach. They offer a number of advantages over conventional oral drug delivery systems, and they are being investigated for a variety of applications [3].

MERITS AND DEMERITS OF GRDDs:

GRDDs offer several merits and advantages, as well as some demerits and limitations, which are important to consider when developing or using this drug delivery approach. GRDDs mainly consists of various merits and demerits for their compositional advancement as below following:

Merits: GRDDs have a number of advantages, but they also have some demerits. The merits of GRDDS as below followings:

- ***Improved Absorption:*** GRDDS can enhance the absorption of poorly water-soluble drugs by maintaining them in the stomach where absorption can occur.
- ***Prolonged Effect:*** They enable sustained drug release, which can result in a prolonged therapeutic effect and less frequent dosing.

- ***Reduced Side Effects:*** Controlled release can also reduce fluctuations in drug levels in the bloodstream, potentially minimizing side effects [2-3].

Demerits: Gastroretentive drug delivery systems have a number of advantages, but they also have some demerits. The demerits of GRDDs as below followings:

- ***Inability to target specific sites:*** GRDDs can be difficult to target specific sites in the stomach, especially if the drug is released slowly. This can be a problem for drugs that need to be released in a specific area of the stomach for optimal absorption or therapeutic effect.
- ***Ineffectiveness for some drugs:*** GRDDs may not be effective for all drugs. For example, drugs that are easily dissolved in stomach acid may not be retained by GRDDs.
- ***Increased risk of side effects:*** GRDDs can increase the risk of side effects from the drug, especially if the drug is released too slowly or too quickly.
- ***Cost:*** GRDDs can be more expensive to develop and manufacture than conventional drug delivery systems [2-4].

GRDDs are a promising technology with the potential to improve the efficacy and safety of oral drug delivery. The demerits of GRDDs before using them for a particular drug.

Table. 01: The merits and demerits of gastroretentive drug delivery systems (GRDDs)

Merits	Demerits
Improves the bioavailability of drugs that are poorly absorbed in the small intestine.	More complex and expensive to develop.
Provides a sustained release of drugs.	May not be suitable for all drugs.
Protects drugs from stomach acid.	May cause side effects, such as nausea and vomiting.
Targets drugs to the stomach.	Less patient compliance.

GRDDs offer several advantages, particularly for drugs with specific absorption challenges or therapeutic requirements [3-6]. The decision to use GRDDs should be based on a thorough assessment of the drug's characteristics, the intended therapeutic goals, patient preferences, and cost-effectiveness.

The main purpose of this review is to provide information on various GRDDs that have been developed to date, as well as the physiological state of the stomach, suitable drug candidates for GRDDs, factors affecting GRDDs, and in vitro and in vivo characterization of GRDDs. In addition, challenges and future perspectives on GRDDs are discussed.

Drug selection criteria for GRDDs:

Selecting drugs for Gastroretentive Drug Delivery Systems (GRDDs) involves considering various factors to ensure that the chosen drug is suitable for such a delivery approach. The key drug selection criteria for GRDDS:

- ***Poor Solubility and Low Permeability:*** GRDDs are particularly useful for drugs with poor solubility and low permeability in the gastrointestinal tract. These drugs often have limited absorption in the upper GI tract, and prolonging their residence time can enhance bioavailability.
- ***Narrow Absorption Window:*** Drugs with a narrow absorption window in the stomach or upper small intestine can benefit from GRDDS. These systems can ensure that the drug remains in the absorption site for an extended period, increasing the chances of absorption [3-4].
- ***pH-dependent Absorption:*** Some drugs exhibit pH-dependent solubility or stability. GRDDS can be designed to release the drug in response to the pH of the stomach, ensuring optimal absorption.
- ***High First-Pass Metabolism:*** Drugs that undergo significant first-pass metabolism in the liver may benefit from gastroretentive delivery. By prolonging exposure in the stomach, the drug can bypass the liver initially, reducing metabolism and increasing systemic bioavailability.

- ***Local Action in the Stomach:*** Drugs intended for local action in the stomach, such as antacids or drugs for treating peptic ulcers or gastroesophageal reflux disease (GERD), are suitable candidates for GRDDS.
- ***Food Interactions:*** Some drugs may interact with food or be affected by changes in gastric pH. GRDDS can be designed to control the release of the drug in the presence of food or to minimize food interactions [3].
- ***Chronic Conditions:*** Drugs used to treat chronic conditions where sustained therapeutic levels are necessary, such as hypertension or diabetes, may be suitable for GRDDS.
- ***Drug Stability:*** The stability of the drug in the gastrointestinal environment is crucial. The drug should remain stable within the GRDDS until it is released at the intended site of absorption.
- ***Toxicity and Side Effects:*** Consideration of potential toxic effects or side effects associated with the drug is important when selecting candidates for GRDDS. Prolonged drug exposure in the stomach or upper GI tract should not lead to increased toxicity [3-5].

These are the same criteria for chosen drug and GRDDS formulation comply with regulatory guidelines and requirements for drug delivery systems.

Table. 02: Drug selection criteria for GRDDS with drugs example

Drug Selection Criteria	Example Drugs selected
Solubility	Poorly soluble in the small intestine but soluble in the stomach: Ranitidine, Metformin
Stability	Stable in the acidic environment of the stomach: Ranitidine, Sucralfate
Absorption	Absorbed in the stomach or upper small intestine: Ranitidine, Ondansetron
Pharmacokinetics	Has a long half-life so that it can be released over an extended period of time: Metformin, Ondansetron
Safety	Safe to be released in the stomach: Ranitidine, Sucralfate
Tolerability	Well-tolerated by patients: Ranitidine, Ondansetron [3-8]

Drug selection for GRDDS should involve a comprehensive evaluation of these criteria to determine the feasibility and potential benefits of using this drug delivery approach. Additionally, collaboration with pharmaceutical scientists, formulation experts, and regulatory professionals is essential in the development process. GRDDS are often used to deliver drugs with a short half-life, as this helps to maintain a constant drug level in the bloodstream [7].

Need or Requirements of GRDDs: There are several reasons why a drug might need to be delivered in a gastroretentive drug delivery system (GRDDs). The most common reasons include as following:

1. ***To improve the bioavailability of the drug:*** Some drugs are poorly absorbed in the small intestine, but are more easily absorbed in the stomach. GRDDs can help to increase the bioavailability of these drugs by keeping them in the stomach for a longer period of time [7-8].
2. ***To provide a sustained release of the drug:*** GRDDs can be designed to release the drug over an extended period of time, which can help to maintain a constant level of the drug in the bloodstream. This can be beneficial for drugs that need to be taken once a day or less.
3. ***To protect the drug from stomach acid:*** The few drugs are sensitive to stomach acid and can be destroyed if they are not protected. GRDDs can help to protect these drugs by keeping them in the stomach for a shorter period of time or by coating them with a layer that protects them from the acid.
4. ***To target the drug to the stomach:*** Some drugs need to be delivered to the stomach to be effective. GRDDS can help to target these drugs to the stomach by making them less likely to be absorbed in the small intestine [5-8].

The specific need for GRDDS will depend on the drug, the patient, and the physician's preferences. The need or requirements for GRDDS depend on the specific characteristics of the drug, the

therapeutic indication, patient preferences, and regulatory considerations. Pharmaceutical companies and researchers often assess these factors to determine whether the development of a gastroretentive drug delivery system is justified and beneficial for a particular drug. The GRDDs is a complex process for the drug delivery and eliminations, the different phases and their timing of the GRDDs motility pattern shown in the given **Table. 03** as below description.

Table. 03: The phases and timing of GRDDS motility pattern respectively

Phases	Description	Timing
Phase I	Liquid phase: The drug is released in the liquid phase of the stomach. This phase is typically very short, lasting only a few minutes.	**Immediately after administration**
Phase II	Dispersion phase: The drug is dispersed in the stomach contents. This phase can last for several hours [06].	**0-3 hours**
Phase III	Floating phase: The drug forms a floating layer on top of the stomach contents. This phase can last for several hours to days.	**0-24 hours**
Phase IV	Adhesion phase: The drug adheres to the lining of the stomach. This phase can last for several days to weeks.	**24-168 hours**
Phase V	Release phase: The drug is released from the dosage form and is absorbed into the bloodstream. This phase can last for several days to weeks [02-09].	**24-168 hours**

GASTRORETENTIVE DRUG DELIVERY SYSTEMS (GRDDs) VS. CONVENTIONAL DRUG DELIVERY SYSTEMS (CRDDs):

Gastroretentive Drug Delivery Systems (GRDDs) and Conventional Drug Delivery Systems (CRDDs) differ significantly in their design, mechanisms of drug release, and applications. GRDDs are specialized drug delivery systems designed to prolong the residence time of drugs in the stomach or upper part of the gastrointestinal tract [8-9]. The primary goal of GRDDs is to enhance drug absorption by maintaining the drug within the gastric region for an extended period. Conventional Drug Delivery Systems refer to the traditional pharmaceutical dosage forms commonly used for drug administration. These include tablets, capsules, syrups, injections, and other forms where the drug is typically released and absorbed throughout the gastrointestinal tract. The diversion in GRDDs and CRDDs mentioned in **Table. 04** as below:

Table. 04: The differences between gastroretentive drug delivery systems (GRDDs) and conventional drug delivery systems (CRDDs) in terms of features

Features	GRDDs Description	CRDDs Description
Purpose	To prolong the residence time of a drug in the stomach.	To deliver the drug to the small intestine as quickly as possible.
Mechanism	Uses various mechanisms to keep the drug in the stomach, such as floating, swelling, mucoadhesion, and magnetic targeting.	Does not use any mechanisms to keep the drug in the stomach.
Drugs	Suitable for drugs that are poorly absorbed in the small intestine, sensitive to stomach acid, or need to be delivered to the stomach.	Suitable for a wider range of drugs.
Side effects	May cause nausea, vomiting, or other side effects due to the harsh environment of the stomach.	Less likely to cause side effects.
Efficiency	More efficient at delivering drugs to the stomach.	Less efficient at delivering drugs to the stomach.
Patient compliance	May be more difficult for patients to take GRDDs consistently due to the need to take them with food or on an empty stomach [7].	CRDDs are easier for patients to take consistently [4-10].

The stomach plays a crucial role in gastroretentive drug delivery systems (GRDDs). The stomach is a muscular sac that is located in the upper abdomen. It is responsible for storing food, breaking it down, and mixing it with gastric juices. The gastric juices contain hydrochloric acid and enzymes that help to break down food.

PHYSIOLOGY OF STOMACH

In gastroretentive drug delivery systems (GRDDs), the stomach plays a crucial role as it is the primary site of drug release and retention. The basic physiology of the stomach of GRDDs involves understanding how the stomach functions and how GRDDs take advantage of these physiological processes.

In the GRDDs, the stomach has a crucial role; therefore, a good understanding of the anatomy and physiology of the stomach is a prerequisite for successful development of the gastroretentive dosage form. The stomach is anatomically divided into two parts: the proximal stomach, which includes the fundus and body, and the distal stomach, which includes the antrum and pylorus, as shown in **Fig. 01.** The stomach's major function is to briefly hold food, grind it, and then gently release it into the duodenum [11]. The fundus and body primarily act as reservoirs for undigested food, whereas the antrum acts as a pump to assist in gastric emptying by a propelling action [12-15]. The stomach's mobility pattern is known as the migrating myoelectric complex (MMC); **Table. 05** shows the several phases of the MMC, stomach emptying happens in both fed and fasted states, however the pattern of stomach emptying differs greatly between the two. In the fasted state, an interdigestive sequence of electrical events follows in a cyclic manner through both the stomach and the small intestine every 90–120 min [16]. The pylorus's diameter rises up to about 19 mm during the interdigestive phase [15–18]. As a result, during the interdigestive phase, particles smaller than the diameter of the pyloric sphincter can easily evacuate from the pylorus to the duodenum [19–20].

Table. 05: The four phases of the migrating myoelectric complex (MMC)

Phase	Description	Duration
Phase I	Quiescent period with virtually no contractions	40-60% of the cycle
Phase II	Intermittent, irregular low-amplitude contractions	20-30% of the cycle
Phase III	Short burst of regular high-amplitude contractions	5-10 minutes
Phase IV	Transitional period back to the quiescence of phase I	10-20 minutes [11-17]

The basic overview of the physiology of the stomach in GRDDs:

Gastric Emptying Time (GRT): The stomach's primary function is to store and process ingested food. After ingestion, the stomach begins to mechanically and chemically digest food. GRDDs is gastric emptying time, which refers to the time it takes for the stomach to empty its contents into the small intestine [14-16]. GRDDs are designed to prolong gastric residence time, ensuring that the drug remains in the stomach for an extended period before progressing to the small intestine. The anatomy of stomach shown in the given Fig. 01.

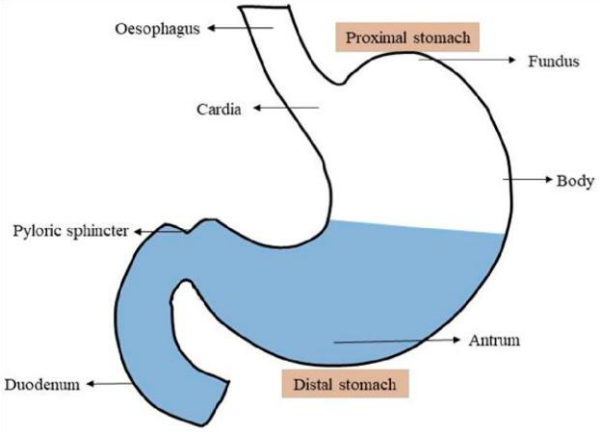

Figure. 01: Schematic view representation of anatomy of stomach

Gastric Secretions: The stomach secretes gastric juices, including hydrochloric acid and pepsin, which help break down food into a semi-liquid mixture known as chyme. GRDDs must be designed to withstand the acidic and enzymatic conditions in the stomach to ensure the drug's stability until it is released at the desired rate.

Motility and Mixing: The stomach's muscular walls contract to mix and churn food with gastric juices, promoting thorough digestion. In GRDDs, especially floating systems, the drug delivery system is designed to float on top of the gastric contents, allowing for consistent mixing and drug release [16].

Food Reservoir: The stomach serves as a food reservoir, allowing the body to receive a continuous supply of nutrients even when food intake is intermittent. GRDDs take advantage of this reservoir function to maintain drug delivery within the stomach.

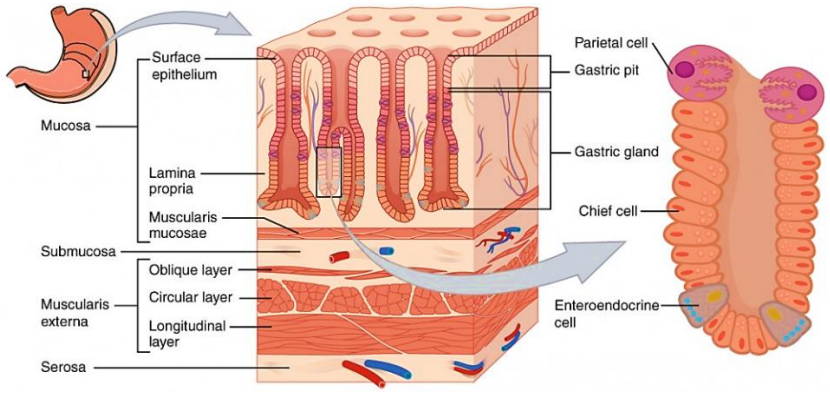

Figure. 02: Schematic view physiology of GRDDs as stomach part

Pyloric Sphincter: The pyloric sphincter is a muscular valve that separates the stomach from the small intestine [15]. In GRDDs, this sphincter can be a point of control, as some systems are designed to delay or control the release of drug formulations into the small intestine by modulating the opening of the sphincter.

Gastric Emptying Variability: Gastric emptying can vary between individuals and is influenced by factors such as the composition of the meal and the presence of disease. GRDDs must account for this variability to ensure consistent drug release profiles [14].

GRDDs leverage the basic physiology of the stomach to achieve their drug delivery objectives. These systems are designed to prolong gastric residence time, control drug release, and ensure drug stability in the stomach's acidic and enzymatic environment. The stomach's role in drug delivery is essential for the successful design and development of GRDDs [15]. There are various factors that affect the performance of gastroretentive dosage forms. These factors are mainly categorized into pharmaceutical factors, physiological factors, and patient-related factors. There are a number of factors that control the gastric retention of dosage forms.

In addition to these factors, the gastric retention of dosage forms can also be affected by the formulation of the dosage form, the manufacturing process, and the storage conditions. The various factors controlling the Gastric retention of dosage forms shown in given **Table. 06** as below description.

Table. 06: The various factors controlling gastric retention of dosage forms

Factors Involving	Description
Size and shape	The size and shape of the dosage form can affect its gastric retention. Larger and more spherical dosage forms tend to float in the stomach, while smaller and more irregular dosage forms tend to sink.
Density	The density of the dosage form can also affect its gastric retention. Denser dosage forms tend to sink, while less dense dosage forms tend to float.
Surface properties	The surface properties of the dosage form can also affect its gastric retention. Dosage forms with hydrophilic (water-loving) surfaces tend to be more easily retained in the stomach. [17-19].
Stomach emptying rate	The stomach emptying rate is the rate at which food and fluids move from the stomach to the small intestine. The stomach emptying rate can be affected by a number of factors, including the type of food or fluid, the presence of food in the small intestine, and the patient's medical condition.
Drug properties	The properties of the drug itself can also affect its gastric retention. Drugs that are poorly soluble in water tend to be more easily retained in the stomach, while drugs that are soluble in water tend to be more easily cleared from the stomach [19-22].

The relative importance of these factors can vary depending on the specific dosage form and the intended use. These are the some factors which affects the GRDDs drug delivery.

CURRENT PHARMACEUTICALS APPROACHES OF GASTROINTESTINAL DRUG DELIVERY SYSTEM (GRDDs)

In this section, we describe currently used gastroretentive drug delivery approaches. The main mechanism of GRDDs includes floating, sinking, swelling, effervescence, mucoadhesion, and magnetic properties. Gastrointestinal drug delivery systems play a crucial role in the effective and targeted delivery of pharmaceutical compounds to the gastrointestinal tract. A brief description for each system is summarized in **Table. 07.** The various approaches and technologies have been developed to optimize drug absorption, increase bioavailability, minimize side effects, and improve patient compliance [18]. The types of GIT System shown in (**Fig. 03**) as below following:

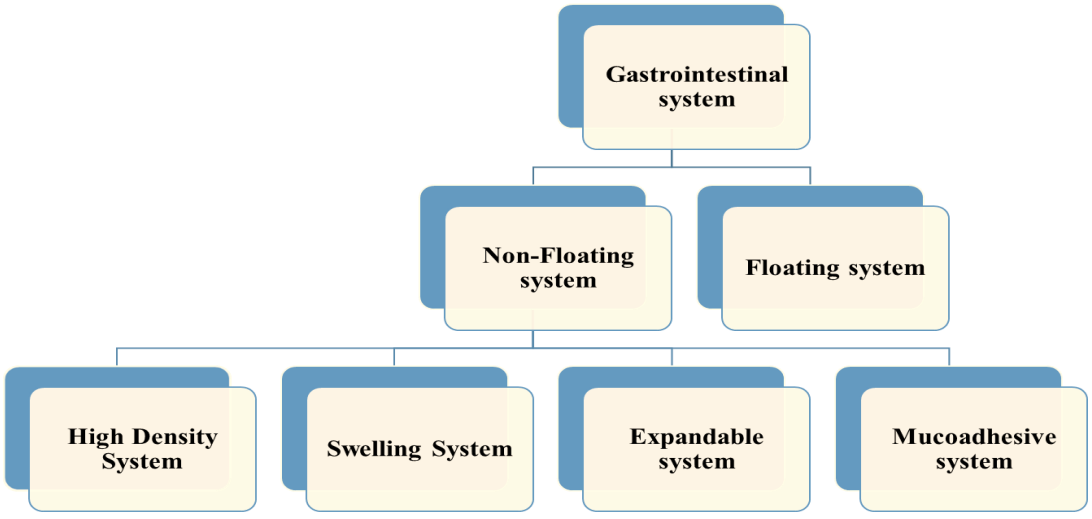

Figure. 03: Schematic flow diagram of the recent approach for GRDDs

The choice of approach for a particular GRDDs will depend on a number of factors, including the properties of the drug, the desired release profile, and the patient's specific needs.

NON-FLOATING SYSTEM

Non-floating drug delivery systems are designed to remain in the stomach for an extended period without floating on the gastric contents. Non-floating systems are a type of gastroretentive drug delivery system (GRDDs) that do not float on the surface of gastric fluid. These systems can be useful for drugs that require prolonged gastric residence time for absorption or therapeutic purposes [19]. The four types of non-floating systems as below following:

1) *High Density System:* High-density systems are designed to have a density greater than that of gastric fluids, ensuring that they sink and remain at the bottom of the stomach. These systems are typically composed of heavy materials or denser polymers. The high-density characteristic allows for prolonged contact between the drug delivery system and the gastric mucosa.

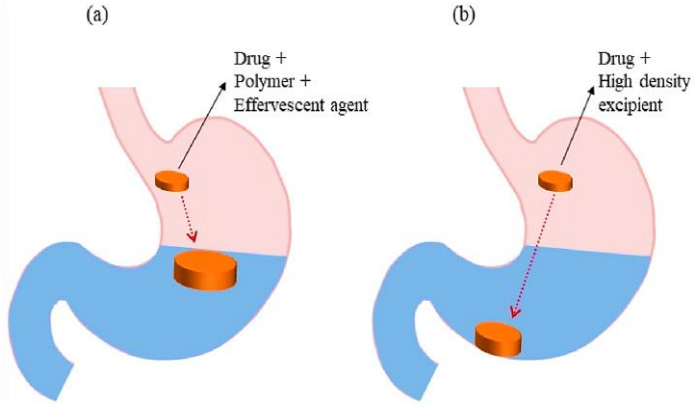

Figure. 04: Schematic representation of GRDDs approach a). Low density and b). High Density approach

Table. 07: The various mechanism of GRDDs [11-26]

Gastroretentive Approach	Mechanism
Low-density systems/ floating systems	System causes buoyancy in gastric fluid. Density of pellets/tablets is lower than the density of stomach fluid.
High density systems	Uses the density of dosage form as a strategy to produce the retention mechanism. Sinking system remains at the bottom of the stomach, where the density of the dosage form is greater than the gastric fluid.
Expandable systems	Expansion of the dosage form occurs by swelling or unfolding in the stomach. Swelling usually occurs because of diffusion. Unfolding takes place due to mechanical shape memory.
Bioadhesive systems	A very complex process with several mechanisms, including electrical theory, adsorption, wetting, diffusion, and fracture theories. The interaction between the negatively charged mucosal surface and positively charged polymers might facilitate the bioadhesive process.
Raft forming systems	The polymer in presence of mono or di valent cations, absorbs water, swells and forms in situ gel layers, which float above gastric fluid and termed as raft.
Magnetic systems	Consists of the small internal magnet mixed with the drug. Its position inside the stomach is controlled by an extracorporeal magnet.
Ion-exchange resin systems	Drug is loaded into the resin to form the resin loaded drug complex, which can be combined with floating delivery or bioadhesive systems.

2) ***Swelling System:*** Swelling systems, also known as superporous hydrogels or swelling-controlled systems, are designed to absorb gastric fluids and swell to a larger size. This swelling prevents the system from passing through the pyloric sphincter into the small intestine. The drug is released as the system swells and gradually erodes [18].

3) ***Expandable System:*** Expandable drug delivery systems (Figure 3a) are designed to have a longer GRT by increasing their volume or form. Initially employed for veterinary purposes, its applications were later expanded to include humans [21]. For the system to function properly, three general designs must be considered: small size for easy oral intake, enlarged form in the stomach to prevent passage through the pyloric sphincter, and size reduction of the system after complete drug release to allow evacuation [6-12]. This system is also termed as a "plug type system" because it has the ability to block the pyloric sphincter. Expandable systems, like swelling systems, expand in size when they come into touch with stomach contents. Expandable systems are specially engineered to expand in a controlled manner, allowing the medicine to be released gradually over time. These systems may consist of a combination of polymers that expand when hydrated [19].

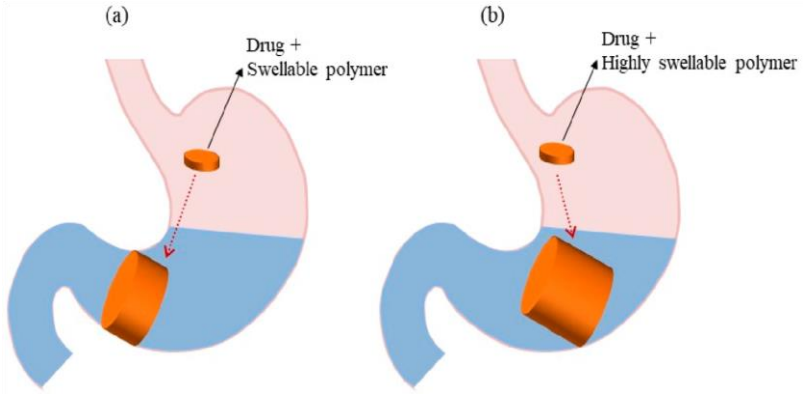

Figure. 05: Schematic representation of GRDDs based non-floating approach

(a) Expandable systems and (b) superporous hydrogel systems.
The various expandable and superporous system in GRDDs generally, consists of drug and swellable polymer and high swellable polymer respectively.

4) ***Bioadhesive/Mucoadhesive System:*** The mucoadhesive/bioadhesive system was first introduced by Park and Robinson in 1984 [26]. It was designed to adhere to the gastric epithelial cell surface and prolong the GRT of drug compounds [21-24]. In this approach, drugs are incorporated in a mucoadhesive agent, which can be either natural or synthetic polymers. Bonding established between the polymer and mucosal surface facilitates the mucoadhesion process. Mucoadhesive systems are designed to adhere to the gastric mucosa, preventing them from being swept into the small intestine. They contain bioadhesive polymers or compounds that interact with the mucosal lining. Mucoadhesion enhances the gastric retention of the drug delivery system, ensuring prolonged contact with the mucosa for drug release and absorption [18-22]. The mucoadhesive properties and interaction strength of the polymer depend on the molecular weight, structure, flexibility of the polymeric chains, hydrogen bonding capacity, cross-linking density, charge, concentration, or hydration degree of the polymer [20].

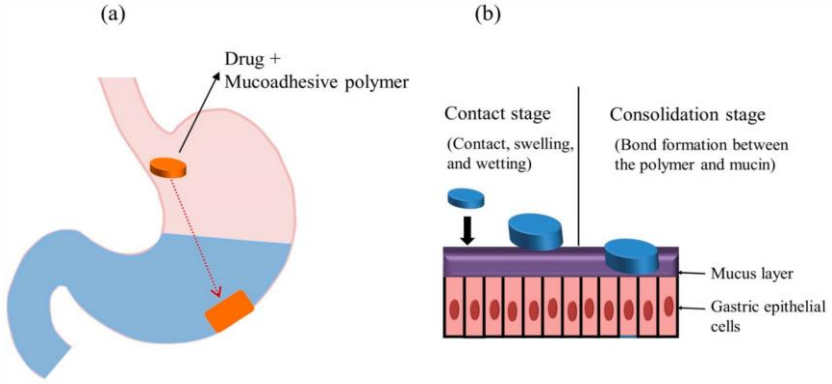

Figure. 06: Schematic view of mucoadhesive GRDDs (a) General representation of mucoadhesive systems and (b) Mechanism of mucoadhesive systems.

The GRDDs mainly consists of various approaches in their delivery and the drug mainly delivery which are mainly on the basis of their several mechanism mentioned in the given **Table. 08** as below description:

Table. 08: The summarizing the theories and suggested mechanisms of mucoadhesion

Theory	Mechanism Involved
Mechanical interlocking	This theory assumes that the mucoadhesive polymer forms physical bonds with the mucin layer. These bonds can be formed by entanglement, interlocking, or bridging.
Electrostatic interaction	This theory assumes that the mucoadhesive polymer and the mucin layer have opposite charges. This attraction can cause the two surfaces to adhere to each other.
Diffusion-interpenetration	This theory assumes that the mucoadhesive polymer diffuses into the mucin layer and forms a network. This network can then adhere to the underlying tissue.
Adsorption	This theory assumes that the mucoadhesive polymer adsorbs to the mucin layer. This adsorption can be caused by van der Waals forces, hydrogen bonding, or hydrophobic interactions.

Non-floating systems has its advantages and can be tailored to suit the specific requirements of the drug being delivered and the therapeutic objectives. They offer the advantage of prolonged gastric residence time and controlled drug release within the stomach, making them suitable for drugs that benefit from these characteristics [21]. The choice of system depends on the drug's physicochemical properties and the desired drug release profile.

FLOATING SYSTEM

Floating drug delivery systems are designed to remain buoyant in the stomach for an extended period, allowing for controlled drug release. These systems are especially useful for drugs that require prolonged gastric retention or absorption in the upper gastrointestinal tract.

Floating systems are a good option for drugs that need to be released in the stomach for a prolonged period of time. They are also a good option for drugs that are sensitive to the acidic environment of the stomach. The several floating GRDDs mainly shown in the (**Fig. 07**) and types of floting approaches in **Table. 09** as below section:

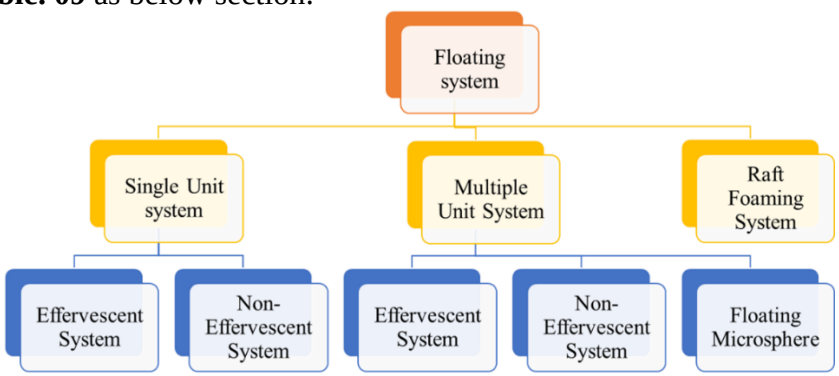

Figure. 07: Schematic flow diagram of the recent approach for the Floating system

The advantages of floating systems as following:
- They can prolong the residence time of drugs in the stomach.
- They can protect drugs from the acidic environment of the stomach.
- They can be used to deliver drugs to a specific location in the stomach.

The disadvantages of floating systems as following:
- They can be difficult to formulate.
- They can be expensive to produce.
- They can cause side effects, such as nausea and vomiting.

Floating systems are a promising technology for the delivery of drugs to the stomach. They offer a number of advantages over conventional oral drug delivery systems, but they also have some disadvantages [26-29]. The choice of floating systems depends on the specific drug and the intended application.

There are several types of floating systems, described as below description:
01. Single Unit Floating Dosage form System: This system consists of a single dosage form, such as a tablet or capsule that floats on the surface of gastric fluid.
a) *Effervescent System (Gas-Generating System):* Effervescent floating systems include a gas-generating agent and volatile liquids. This approach has been applied for single- and multiple-unit systems. In the gas-generating floating system, effervescent agents such as sodium bicarbonate, calcium carbonate, tartaric acid, and citric acid are used in combination with hydrophilic polymers. Effervescent systems generate gas within the stomach, creating buoyancy and causing the dosage form to float. These systems typically contain a combination of a drug, a gas-generating agent (e.g., sodium bicarbonate), and a polymer matrix. As the gas is generated, it pushes the system to the top of the gastric contents, where it remains while slowly releasing the drug [20-22].
b) *Non-Effervescent System:* In non-effervescent systems, highly swellable cellulose derivatives or gel-forming polymers are used [5]. The formulation technique of non-effervescent systems involves mixing the drug with a gel-forming polymer. Various non-effervescent systems include the hydrodynamically balanced system (HBS), single- and double-layer floating tablets, and microballoons/hollow microspheres. Non-effervescent floating systems rely on the inherent buoyancy of the dosage form or the use of low-density materials. These systems may incorporate hydrophobic or porous polymers that reduce the density of the dosage form. The natural buoyancy allows them to float on the gastric contents for an extended period.
02. Multiple Unit Floating Dosage Form System
A. *Non-Effervescent System:* Similar to single unit non-effervescent systems, multiple unit non-effervescent systems use low-density materials or hydrophobic polymers to achieve buoyancy. These systems consist of multiple smaller units that collectively provide prolonged gastric retention.
B. *Effervescent System (Gas Generating System):* Multiple unit effervescent systems generate gas within the stomach, collectively causing the units to float. Each unit contains a gas-generating agent, drug, and polymer matrix. The generated gas collectively keeps all units afloat, ensuring extended gastric residence [22-26].

Table. 09: The various types of non-floating GRDDs with drug examples

Type of GRDDs	Description	Drug Example
Single-unit GRDDs	This is the simplest type of GRDDs. It consists of a single dosage form that contains the drug and the buoyancy system.	Aspirin, diclofenac sodium, metoprolol.
Multiple-unit GRDDs	This type of GRDDs consists of multiple dosage forms that are linked together. The dosage forms can be of the same or different sizes [21].	Metoclopramide, ranitidine.
Raft GRDDs	This type of GRDDs is made up of a single layer of dosage forms that are floating on the gastric fluid. The	Domperidone, lansoprazole.

	dosage forms are typically small and have a high surface area to volume ratio.	
Hollow GRDDs	This type of GRDDs is made up of a hollow dosage form that is filled with a gas or liquid. The gas or liquid makes the dosage form buoyant [22].	Griseofulvin, ketoprofen.

03. Hollow Microspheres: Hollow microspheres are small, spherical particles with a hollow core that can be filled with drug. These microspheres are typically made from materials that are less dense than gastric fluids, allowing them to float. The hollow core may be filled with gas or air, further enhancing buoyancy.

04. Raft Foaming System: Raft-forming systems are another type of GRDDs, formulated with effervescent excipients and gel forming polymers in order to achieve the sustained drug delivery. Figure 5 illustrates the concept of these systems, which mainly focuses on achieving localized effects because floating rafts act as blockades between esophagus and stomach. Thus, they can be used for the effective management of gastric esophageal reflux disease. When raft-forming systems come into contact with gastric fluid, they swell and form a viscous cohesive gel leading to the formation of a continuous layer termed as rafts.
Raft foaming systems are designed to create a floating, gel-like layer on top of the gastric contents. They typically consist of antacids and polymers that foam upon contact with gastric acid. [23-25].

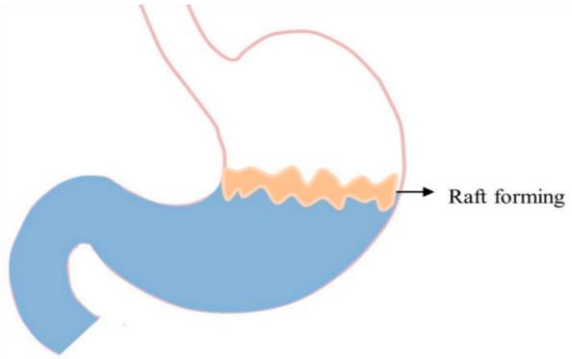

Figure. 08: Schematic view of GRDDS based on raft-forming systems

The common differences in floating and non-floating GRDDs discussed in Table. 10 as below.

Table. 10: The differences between floating and non-floating GRDDs

Feature	Floating GRDDs	Non-floating GRDDs
Mechanism of action	Float on the gastric fluid due to their lower density	Adheres to the stomach lining or expands in the stomach
Drug delivery	Sustained release of drug	Controlled release of drug
Applications	Drugs that are sensitive to the acidic environment of the stomach, drugs that need to be delivered in a controlled manner	Drugs that are not sensitive to the acidic environment of the stomach, drugs that need to be delivered to a specific site in the stomach
Examples	Esomeprazole delayed-release capsules (Nexium), ranitidine bismuth citrate (Tritec)	Domperidone (Motilium), lansoprazole (Prevacid), ketoprofen delayed-release capsules (Orudis KT) [25]

There are a number of advanced approaches to gastrointestinal drug delivery systems (GRDDs). The several most common promising approaches include:

Table. 11: Advance approaches of gastrointestinal drug delivery system (GRDDs)

Approach	Description
Floating systems	These systems use a floating agent, such as a surfactant or a polymer, to keep the dosage form buoyant in the stomach.
Swelling systems	These systems swell in the stomach due to the absorption of water. This swelling can help to keep the dosage form in the stomach for a longer period of time [27].
Mucoadhesive systems	These systems adhere to the lining of the stomach. This adhesion can help to keep the dosage form in the stomach for a longer period of time.
Magnetic targeting systems	These systems use magnets to target the dosage form to a specific region of the gastrointestinal tract.
Bioadhesive systems	These systems use bioadhesive polymers to attach to the lining of the gastrointestinal tract. This adhesion can help to keep the dosage form in the stomach for a longer period of time and also protect the drug from degradation by stomach acid.
Osmotic pump systems	These systems use an osmotic pressure gradient to deliver the drug at a controlled rate [28].

Gastrointestinal Drug Delivery Systems (GRDDs) have evolved significantly over the years to enhance drug bioavailability, reduce side effects, and improve patient compliance. Advanced approaches in this field continue to emerge, offering innovative solutions for effective drug delivery to the gastrointestinal tract. These are the some of them basic approach for the GRDDs drug delivery.

Gastrointestinal drug delivery systems offer a wide range of options for optimizing drug therapy, improving patient outcomes, and reducing the limitations associated with conventional oral drug administration.

CURRENT STATUS OF GRDDS IN MARKETED BASIS:

The current status of GRDDs in the marketed basis is that there are a number of GRDDs that are approved and marketed for use in humans. These GRDDs are used to deliver a variety of drugs, including anti-ulcer drugs, anti-emetic drugs, and anti-inflammatory drugs.

Table. 12: The GRDDs that are currently marketed, along with the disease they are used to treat and the drug

Disease	Drug	GRDDs Type
Gastroesophageal reflux disease (GERD)	Esomeprazole	Floating capsule
Ulcers	Ranitidine bismuth citrate	Floating tablet
Nausea and vomiting	Domperidone	Mucoadhesive tablet
Pain and inflammation	Ketoprofen	Expandable capsule
Fungal infections	Griseofulvin	Hollow microsphere [28-30]

There are a number of current advancements in GRDDs. The various advancements includes:

- The development of new polymers and materials that can be used to make GRDDs. These new materials can be designed to have specific properties, such as buoyancy, swelling, or mucoadhesion. There are a number of new polymers and materials that are being developed for use in GRDDS. These materials include:

– ***Hydrogels:*** Hydrogels are cross-linked polymers that can absorb water. They are used to make floating GRDDS.

- ***Biodegradable polymers:*** Biodegradable polymers are polymers that can be broken down by the body. They are used to make GRDDs that can be eliminated from the body without the need for surgery.
- ***Magnetic polymers:*** Magnetic polymers can be used to make GRDDs that can be targeted to specific areas of the stomach using a magnetic field.

- The development of new manufacturing techniques that can be used to produce GRDDs with high precision and reproducibility. There are a number of new manufacturing techniques that are being developed for GRDDs. These techniques include:
- ***3D printing (3DP):*** 3D printing is a technique that can be used to create complex structures. It is being used to develop GRDDs with specific shapes and sizes.
- ***Microencapsulation:*** Microencapsulation is a technique that can be used to encapsulate drugs in a protective layer. It is being used to develop GRDDs that are protected from the acidic environment of the stomach.

- The development of new in vitro and in vivo methods for evaluating GRDDs. These methods can be used to assess the performance of GRDDs, such as their gastric retention time, drug release profile, and biodistribution [31-35]. There are a number of new in vitro and in vivo methods that are being developed for evaluating GRDDs. These methods include:
- ***Gastric emptying studies:*** Gastric emptying studies are used to measure the rate at which drugs are emptied from the stomach. They are used to assess the gastric retention time of GRDDs.
- ***Drug release studies:*** Drug release studies are used to measure the rate at which drugs are released from GRDDs. They are used to assess the drug release profile of GRDDs.
- ***Biodistribution studies:*** Biodistribution studies are used to track the movement of drugs in the body. They are used to assess the targeting ability of GRDDs [32-33].
  The development of these new technologies is making it possible to develop GRDDs that are more effective, patient-friendly, and targeted. The commonly known GRDDs products and technologies include as below following:
- ***Gaviscon:*** Gaviscon is an over-the-counter (OTC) antacid medication that uses a floating mechanism to create a raft in the stomach, providing relief from heartburn and acid reflux. It is designed to stay in the stomach and form a protective barrier against stomach acid.
- ***Acuform:*** Acuform is a patented drug delivery technology developed by Ethypharm. It is used in various medications to provide controlled and prolonged drug release in the stomach. The technology relies on a swellable, hydrophilic polymer matrix to enhance gastric retention.
- ***Sustained-Release Proton Pump Inhibitors (PPIs):*** Some proton pump inhibitors, such as Dexilant (dexlansoprazole), use GRDDS technology to provide extended release of the active ingredient for the treatment of conditions like gastroesophageal reflux disease (GERD) and peptic ulcers.
- ***Gastrocoat:*** Gastrocoat is a gastroretentive drug delivery system used in the formulation of medications to treat gastric ulcers and related conditions. It helps to prolong the contact time of the drug with the gastric mucosa.
- ***Swelling Systems:*** Various pharmaceutical companies have developed GRDDs based on swellable systems, where the drug dosage form swells upon contact with gastric fluids, helping it to remain in the stomach for an extended period [34].

The choice of GRDDs depends on a number of factors, including the drug being delivered, the desired drug release profile, and the patient's individual needs. The various commercial products in GRDDs used with various delivery system below **Table. 13** as following:

Table. 13: The various gastroretentive products available in the market [21-28]

Product Name	Dosage Form	Mechanism of Action	Indications
Esomeprazole delayed-release capsules	Capsule	Forms a gel layer in the stomach that slows down gastric emptying	Gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome
Lansoprazole delayed-release capsules	Capsule	Forms a gel layer in the stomach that slows down gastric emptying	GERD, Zollinger-Ellison syndrome
Pantoprazole delayed-release capsules	Capsule	Forms a gel layer in the stomach that slows down gastric emptying	GERD, Zollinger-Ellison syndrome
Rofecoxib delayed-release tablets	Tablet	Binds to COX-2 enzymes in the stomach and inhibits the production of gastric acid	Pain relief, inflammation
Sucralfate suspension	Suspension	Forms a protective layer on the lining of the stomach that helps to prevent erosion	Duodenal ulcers, gastric ulcers
Misoprostol tablets	Tablet	Stimulates the production of mucus in the stomach and intestines that helps to protect the lining.	Prevention of NSAID-induced ulcers

GRDDs have several advantages over conventional oral drug delivery systems. They can improve the bioavailability of drugs that are unstable in the alkaline environment of the small intestine, or that have a narrow absorption window. They can also be used to deliver drugs to the stomach for local treatment, such as for ulcers or gastritis [35]. Additionally, GRDDs can help to reduce the frequency of dosing, which can improve patient compliance.

FUTURE PERSPECTIVES OF GRDDS

The GRT of the conventional dosage form is one of the main challenges in the pharmaceutical industry, especially for drugs that are absorbed from the upper part of the intestine. Developing GRDDS will help to overcome the drawbacks associated with conventional dosage form, although further work is needed on its shortcomings. To date, many studies have been performed on GRDDS utilizing the single system approach such as floating, expandable, and mucoadhesive systems [37]. The future perspectives of GRDDS are promising. With continued research and development, GRDDS can be used to improve the delivery of drugs to the stomach in a number of ways.

The future perspectives of GRDDS as below followings:

- ***Improved drug bioavailability:*** GRDDS can be used to improve the bioavailability of drugs by preventing them from being degraded by gastric acid or enzymes. This can be done by using floating systems, mucoadhesive systems, or osmotic systems.
- ***Extended drug release:*** GRDDS can be used to extend the drug release time by preventing the drug from being released too quickly. This can be done by using osmotic systems or magnetic systems [30-38].
- ***Targeted drug delivery:*** GRDDS can be used to deliver drugs to a specific location in the stomach. This can be done by using magnetic systems or bioadhesive systems.
- ***Reduced side effects:*** GRDDS can be used to reduce the side effects of drugs by preventing them from being absorbed too quickly or by delivering them to a specific location in the stomach.
- ***Improved patient compliance:*** GRDDS can be made more convenient and easy to take, which can improve patient compliance. For example, GRDDS can be made into chewable tablets or capsules that are easier to swallow [33-36].

GRDDS are a promising new technology with the potential to improve the treatment of a wide range of diseases. With continued research and development, GRDDS can revolutionize the way drugs are

delivered to the stomach. The challenges that need to be addressed in order to realize the full potential of GRDDS:

- ***Stability:*** GRDDS need to be stable in the harsh environment of the stomach. This can be a challenge, as many polymers and other materials used in GRDDS are degraded by gastric acid and enzymes.
- ***Biocompatibility:*** GRDDS need to be biocompatible, meaning that they should not cause any harm to the stomach lining. This is important, as the stomach lining is a very delicate tissue.
- ***Manufacturing:*** GRDDS need to be manufactured in a cost-effective way. This is a challenge, as GRDDS often require specialized equipment and techniques.
- ***Clinical trials:*** GRDDS need to be tested in clinical trials to demonstrate their safety and efficacy. This is a long and expensive process, but it is essential to ensure that GRDDS are safe and effective for human use [32-38].

The future of GRDDS is bright. With continued research and development, GRDDS have the potential to revolutionize the way drugs are delivered to the stomach and improve the treatment of a wide range of diseases.

The development of GRDDs is a promising area of research. With continued research, GRDDs could be used to deliver a wider range of drugs more effectively and safely.

CONCLUSION

Gastro retentive drug delivery systems are the most preferable systems in order to deliver the drugs which have a narrow absorption window near the gastric region. A growing variety of drug delivery systems are being created 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. Even though a number of GRDDS, including bio/mucoadhesive, magnetic, low, and high-density systems, have been described in the literature, further research is still needed 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. The physiological processes that occur in the GIT must be taken into account, along with the proper medication and excipient combinations and formulation techniques. Based on the literature surveyed, we concluded that Gastro retentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption. The conclusion of this review had completely over view of GRDDS delivery with their recent advances and marketed products.

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