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Gastro-retentive drug delivery technologies and their applications with cardiovascular medications

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ABSTRACT

Many trials have recently been conducted to increase drug absorption and the efficacy of oral dose formulations (DFs). Various technologies have been developed in recent years to solve physiological obstacles such as changes in gastric retention and emptying time by researching and developing controlled-release oral medication delivery systems. To develop therapeutic drug efficacy, medicines that display a window type of absorption, have stability problems at basic pH, have high solubility in the acidic environment, or which are locally active in the gastric medium can be loaded into gastroretentive drug delivery systems (GRDDSs). For the past three decades, (GRDFs) have been developed. Historically, they were intended for veterinary medicine, but the design was later modified to improve human medication treatment. Sustained oral-release Gastroretentive dosage forms have several benefits for pharmaceuticals which are absorbed through the upper gastrointestinal system, and they increase the bioavailability of treatments with a narrow absorption window. Expandable systems, mucosal adhesive systems, ultra-porous floating systems, high-density systems, magnetic systems, and hydrogels, are among the strategies described in this review to lengthen stomach residency time. The current study discusses some cardiovascular medications that could benefit from gastroretentive methods, as well as the elements that determine gastric retaining time and how gastroretentive systems work.

Keywords: *physiological, system, current, study*

INTRODUCTION

Traditional drug delivery systems (DDSs) that are used orally have several advantages in human medicine, including the convenience of use, formulation flexibility, cost-effectiveness, low storage needs, and high patient compliance. Nonetheless, because of the multiplicity of the gastrointestinal tract (GIT), low bioavailability, stomach pH, gastric retention time, surface area, and enzymatic activity, these systems encounter problems associated with many drugs[1]. They may also be unable to deal with gastrointestinal difficulties such as partial medication release, reduced drug effectiveness, frequent dosage, and failure to hold the medicines in the stomach for a long time.

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As a result of the aforementioned circumstances, the development of GRDDSs became urgent, Due to their significant therapeutic benefits, expandable GRDDs have been developed throughout the previous three decades. They were primarily designed for veterinary purpose and was later modified for improved human medication therapy[2], [3]. Indeed, such methods outperform traditional systems in terms of improving the bioavailability of pharmaceuticals that have a lower GIT window of absorption, are unstable, or have solubility problems at high pH, drugs have a short half-life, and are active in the upper GIT. GRDDSs can also be used to improve drug delivery rate control by constantly releasing the medication to the appropriate absorption point and at the required times over a long period until the medication has been released entirely from the dosage form[4], [5]. For more than three decades they began to study delivering the drug to a specific site (e.g. stomach), Under the generic term "controlled release systems," release the active drug to a specific point or close to so-called "absorption windows" or for local treatment can also be taken into account[6]. Also, S.S. Davis studied the gastrointestinal transit of pellets and tablet and their relation to food intake[7]. After that Dressman J, discussed the physiological factors that affect gastrointestinal absorption that help in developing GRDDS[8]. Currently, the GRDDSs are fabricated in various designs to extend the residency time of drugs in the stomach, as illustrated in (Fig. 1)[4], [9].

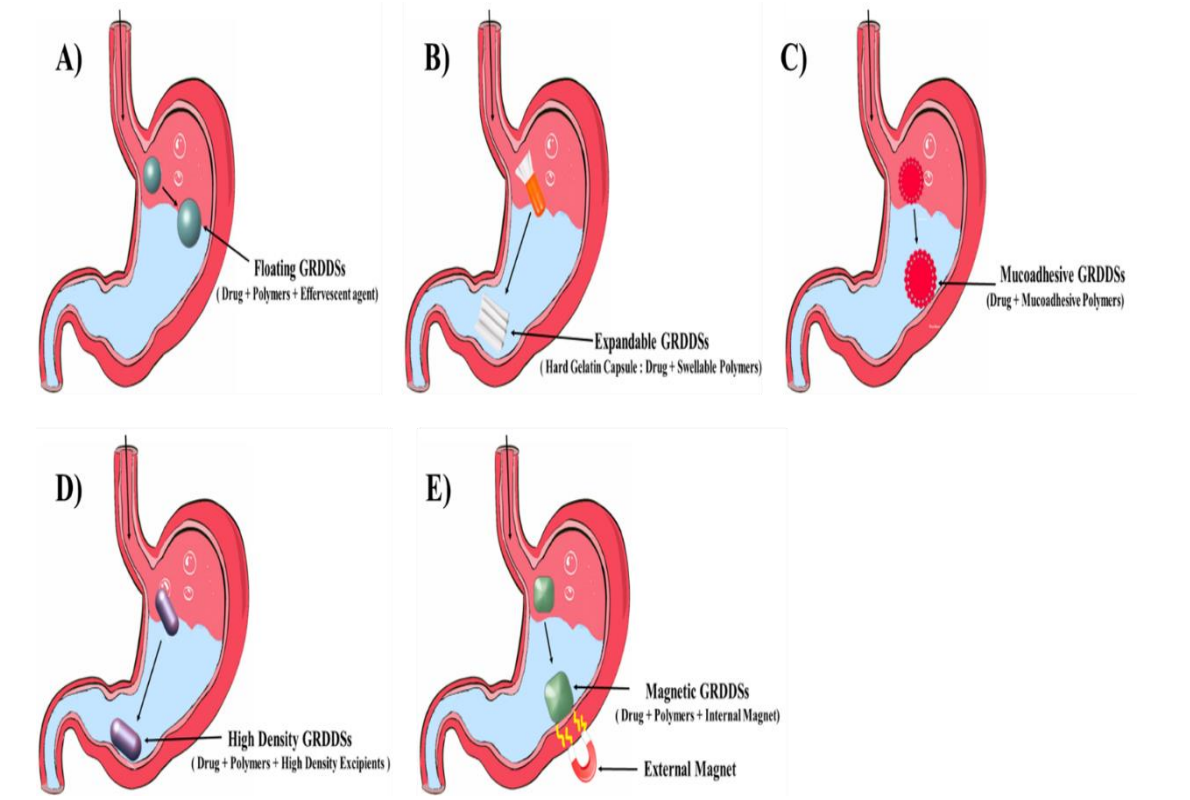

FIG. 1: Examples of different types of GRDDS.

Moreover, scientists have conducted extensive research work to prepare and evaluate various gastro retentive systems, some examples along with the aim of the preparations are described in Table 1.

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TABLE 1: Some Examples of GRDDSs

GRDDSs	Medication	Purpose of the formulation	Reference(s)
Expandable DDS based on shape memory polymers	Allopurinol	Improve bioavailability (the drug has a window absorption.	[10]
Mucoadhesive and floating DDS	Amoxicillin	Improving therapeutic effect	[11]
Swellable and floating GRDDS	Ciprofloxacin	Improved drug delivery to the absorption site	[12]
Floating-Bioadhesive Microparticles	Clarithromycin	Increase the efficacy of the drug	[13]
Mucoadhesive sustained release	Itraconazole	Improve oral bioavailability	[14]
Floating-Bioadhesive Microspheres	Acetohydroxamic acid	Evaluate the effectiveness of the medication.	[15]
Unfolding polymeric membrane	Levodopa	Maintain sustained therapeutic level.	[16]
Expandable system	Levetiracetam	Give sustained release	[17]
Expandable dosage form	Acetaminophen	Increase gastric residence time and release the drug slowly.	[18]
Expandable system	Gabapentin	Controlled drug release and decreased side effects.	[19]

The complicated motility of the stomach and food effects have a vital influence on the gastric retention behavior of floating systems[20]. About expandable systems, Polymers that are hydrolyzable and biodegradable present storage problems. Short-lived mechanical shape memory thus making it tough and costly[21], [22]. When opposed to other systems, one of the limitations of magnetic systems is the need for an external device. It must be carefully utilized and precisely positioned to facilitate medicine release in the appropriate location while avoiding discomfort for the patient[23]. Related to high-density systems, Producing high-density pellets with considerable concentrations of medication is technically challenging [4]. In summary, the drawbacks are illustrated in Table.2.

TABLE 2: Disadvantages of GRDDs [24]

Used technology	Disadvantages
High-density systems	Due to technical issues, significant quantities of the medicine cannot be manufactured.
Floating systems	The amount of fluid required in the gastric region is highly dependent on the stomach's fed state. Floating lag time
Expandable systems	Hydrolyzable, biodegradable polymers cause storage issues. Mechanical form memory with a short lifespan. Producing it is difficult and expensive.
Mucoadhesive systems	The efficiency of a mucus system can be harmed by high mucus turnover. It may bond to other mucosal linings, such as the esophagus.
Magnetic systems	Patient compliance may be jeopardized.

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Stomach Physiology

Because the stomach plays such a key part in the GRDDSs, knowing stomach anatomy and physiology is essential for efficient formulation development. In an adult, the most dilated unit of the digestive tube is the stomach, Having a maximum capacity of 1000–1500 ml. It is located between the esophagus and the duodenum, which is the initial portion of the small intestine. The stomach's primary purpose is to combine food with acid, mucus, and pepsin, then release the resulting chyme into the duodenum at a controlled rate for absorption. Both neuronal and hormonal inputs influence gastric motility [25], [26]. The stomach is separated into two-compartment anatomically: the proximal stomach and the distal stomach, the fundus, and the body of the stomach are located in the proximal stomach, and the distal stomach contains the pylorus and antrum (Fig. 2). The fundus and body are mostly employed to hold undigested food, while the antrum works like a pump, assisting stomach emptying through pushing action[26]. The migrating myoelectric complex (MMC) is the pattern of stomach motility[27]; several stages of the MMC are depicted in (Fig. 3).

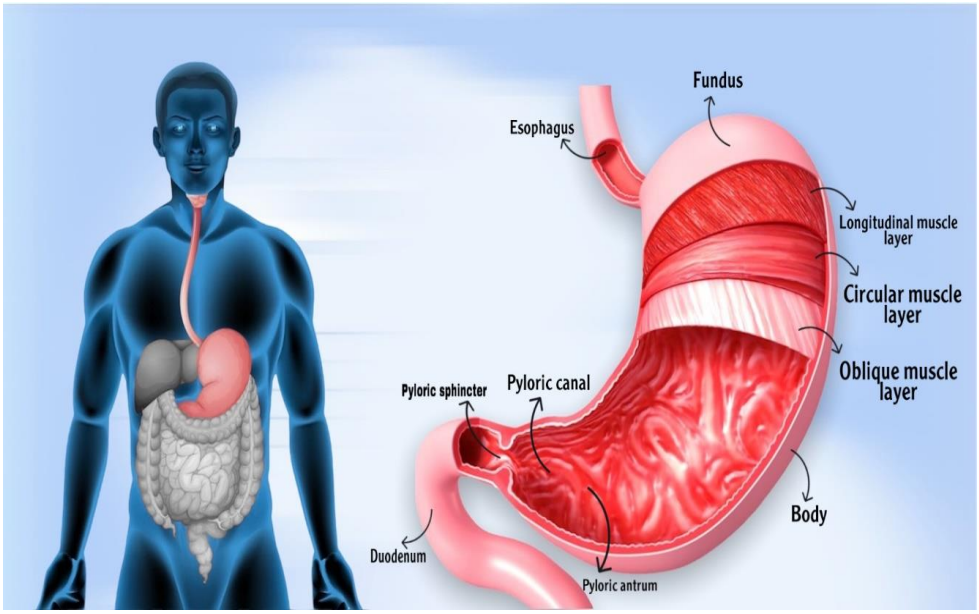

FIG. 2: Stomach anatomy.

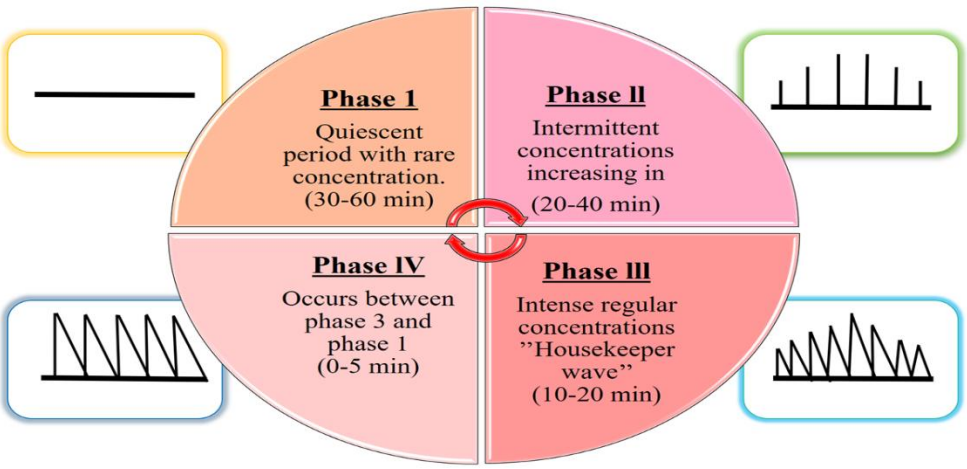

FIG.3: MMC and stomach motility pattern.

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Stomach emptying can occur in fed and unfed statuses, however, the sequence of gastric emptying differs significantly [26]. Fasting causes an inter-digestive advancement of the electrical process to occur every 90 to 120 minutes via the stomach and small intestine. The pylorus expands to about 19 mm in diameter during the inter-digestive process. During the inter-digestive phase, this results in units that are small in size than the diameter of the pyloric sphincter and empty easily from the pylorus to the duodenum. Though the fed condition, motor action begins 5 to 10 minutes after meal ingestion and continues as long as the food stays in the stomach, this can disrupt the gastric emptying rate (GRE)[25], [26], [28].

Influences Affecting GRDDS Efficacy

Some properties of a gastro-retentive system can be affected by several formulation factors like polymer kinds, for example (nonionic, cationic, and anionic polymers), the concentration of polymer in GRDDs, a molecular weight of the polymer, viscosity, and drug solubility. Furthermore, excipient physicochemical properties play an essential role in several GRDDS [29]. A summary of factors affecting GRDDS is presented in Fig. 4.

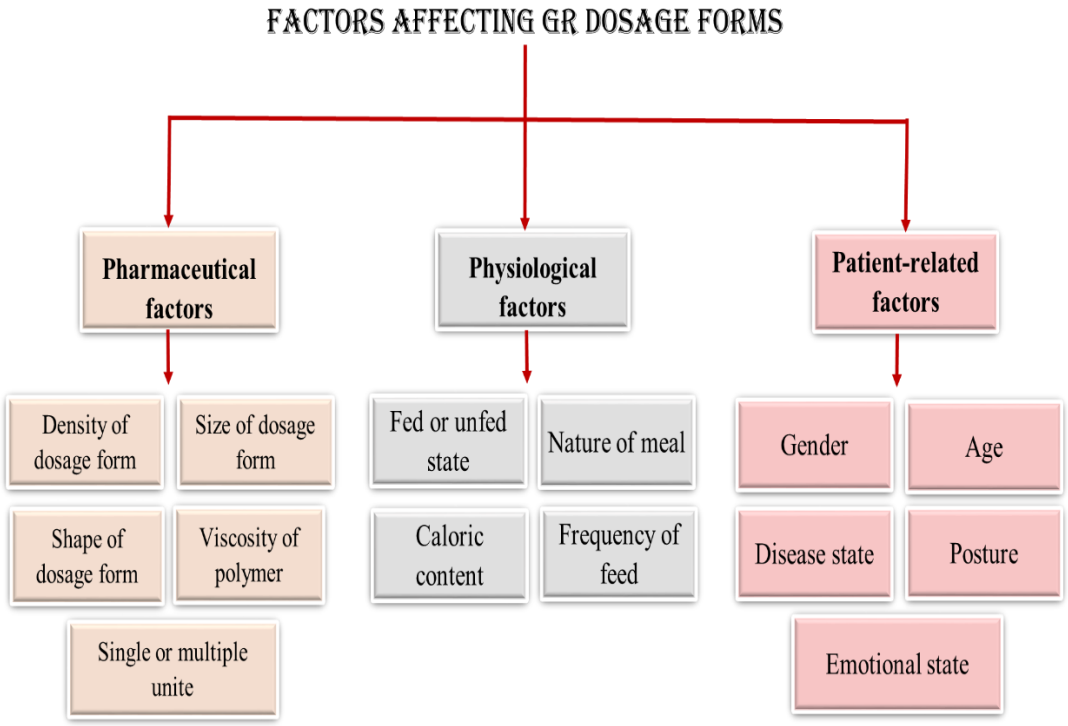

FIG 4. Factors affecting GR dosage forms.

Pharmaceutical aspects

To get a proper preparation for GRDDS, it is critical to comprehend the significance of excipients and polymers, in different systems of GRDDS. Like expandable dosage forms, polymers that have a great swelling ratio are favorable. In addition, molecular weight, polymer viscosity, and physicochemical properties can also have a significant role in the formulation of the GRDDs [29].

GRDDs density

The density of the different systems is a physical characteristic that has two opposing effects on stomach retention time: floating and sinking. The dosage form in the first case has a lower density than the gastric juice, namely less than (1.004 g/cm3) [30].

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As floating capacity increases, the chances of a prolonged retention duration and the reduction of the presence of food effect are increased [20].

An increase in stomach residence time could also be caused by a change in the dosage form's density. A density of roughly 2.5g/cm3 is necessary to make this impact significant [31].

The effect size of the dosage form on GRDDs

For non-floating systems, the dosage form size is a variable that can be modified to prolong the stomach residence duration. For the systems that are non-disintegrating, an increase in the size of dosage form greater than the diameter of the pyloric sphincter (about 12.8 ±7 mm in humans) seems rational. This will lead to blocking it from reaching the duodenum, lengthening the time it spends in the stomach; this will last as long as the digestion phase[4][32][33].

In addition to that, the shape of the dosage unit is also important, for example, ring shape dosage forms, and tetrahedron-shape dosage forms have a prolonged residence time in the stomach in comparison to other shapes[32], [34].

Physiological Factors

Extrinsic factors such as the meal's nature, caloric intake (calorie densities and type), frequency of consumption, position, sleeping, and physical activity level have been shown to impact the GRTs of medications in the stomach in several investigations [35], [36].

The MMC, which occurs every 90 to 120 minutes in fasting states, represents gastrointestinal motility. Mechanical activity washes undigested food from the gastric cavity during this time. If the time of administration occurs simultaneously with the MMC, the GRT of the formulation will be quite short. An MMC is disrupted and waves (called housekeeper waves) are not formed if the food is found in the stomach, resulting in a prolonged GRT [28], [37].

Patient-Related Factors

GRDDSs can be influenced by characteristics of patients such as sex, age (older patients have a longer GRT), sickness, and emotional state. Gender affected the time of gastric emptying and intraluminal pH. Slower stomach emptying times occur in females than in males[38]. Hormonal effects could explain why females have a longer GRT than males. Males released more stomach acid than females, according to another study[39]. Similarly, the GRT is influenced by the patient's age. When compared to younger people, elderly persons have a longer GRT [38]. The nature of the patient's disease can also affect the GRT of the dosage units. Patients who have Parkinson's disease, for example, exhibit a long GRT with often constipation [40]. The patient's mental state appears to have an important role in the determination of the stomach residence duration, some researchers found when the patient is in a low emotional state, there is decreasing in gastric emptying time, whereas the opposite is observed in a person feeling anxiety [41].

GRDDS's Current Pharmaceutical Technologies

Floating, sinking, swelling, effervescence, mucoadhesion, and magnetic characteristics are the major mechanisms of GRDDSs [32].

Drug delivery system with high-density mechanism (Sinking)

This method entails covering the medicine on a dense core or blending it in the presence of inert elements like powder of iron, zinc oxide, BaSo4 (barium sulfate), and titanium oxide to make the formulations denser than the normal stomach content. The density of these materials rises to about 1.5-2.4 gm/cm. The transit time of such pills in the gastrointestinal tract can be prolonged to about 5.8 to 25 hrs. depending on density. Although no evidence of this system's efficacy in humans has been found, and no formulation has been advocated [42].

Super porous hydrogels

The structure of super-porous hydrogels is made up of hydrophilic polymers (that are crosslinked) and have the ability to absorb large water amounts and other aqueous preparation fastly and

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swell to enough size, the final result is structured having many large and huge pores that are joined together resulting in open channel design [43], [44]. Capillary action provides water uptake into the dry system. The rapid swelling, which takes about 20 minutes, aids to prevent the emptying of stomach content early which is caused by waves called housekeeping waves, resulting in extending the gastric residency period [2]. However, because completely swelled super-porous hydrogels are mechanically very fragile, so to make these technologies resistant to digestive contractions, they must have a specified mechanical strength [45]. To maintain mechanical strength, super-disintegrant agents like (Ac-Di-Sol1, sodium starch glycolate (Primojel), Explotab, and crosslinked polyvinylpyrrolidone) were used to formulate super-porous hydrogels [46].

Bio/mucoadhesive systems

Since Park and Robinson first proposed bioadhesion as a new technique for controlling drug delivery aims in 1984, it has been widely applied to the development of efficient and regulated drug delivery systems. The great effort to discover and develop new polymers with bioadhesion properties for multiple delivery routes, such as ocular, oral, vaginal, and nasal, demonstrates this interest [47], [48]. Mucoadhesive methods increase the length of contact between medication and human biological membranes which results in extended residence time of the drug in the stomach[4]. Bioadhesive polymers can stick to biological membranes and tissues and might be natural or manufactured. Based on the type of bond formed between the epithelial membrane and the polymer used, they are classified as cyto-adhesive or mucoadhesive. The cyto-adhesive property relates to the polymer's ability to adhere to a layer of epithelial cells, which is accomplished by reaction with cell- receptors, whereas the mucoadhesion means binding to the mucus layer and not to cells [49].

Both of these features can be found in some polymers. Chitosan, Poly (acrylic acid), tragacanth, cholestyramide, sodium alginate, hydroxypropylmethylcellulose, Carbopol, sucralfate, Sephadex, poly (alkyl cyanoacrylate) polyethylene glycol, and dextran, are examples of polymers often utilized for bioadhesion [50].

Floating systems

Floating systems are the most well-known of the gastroretentive systems mentioned in this review. Such systems have a low density which is about or less than 1.004g/ml, so they can remain floating above the stomach content without impacting the gastric emptying rate[51]. This feature permits the floating preparation to float in the stomach cavity for an extended duration, allowing the medicine to be delivered at the anticipated rate during the residence duration of the systems in the stomach [52]. The force of floating and the stomach content determine the time of discharge of the system from the stomach [53].

Non-effervescent floating method

The system float in two ways with the non-effervescent method. A blend of large swelling and gelling capability polymers, such as polysaccharides, hydrocolloids (type of cellulose), and matrix-making polymers, such as polycarbonate, polymethacrylate, hydroxypropylmethylcellulose, polyacrylate, and sodium alginate, is employed in the first one [54]. These systems inflate due to hydration once they reach the gastric juice, generating a layer of gel with entrapped air surrounding the core of the system, which limits the release of medication. The system's floating capacity is provided by the trapped air [54].

The effervescent floating systems

An example of this system is a system-generated gas and system containing volatile liquid. When the gastric juice or acid in the formulation (like citric acid and tartaric acid) reacts with bicarbonate or carbonate presented in the formulation, the result is a gas-generating system [43]. The hydrocolloid gel matrix entrapped the gas that will form, which leads to influencing the drug release profile. Adding bicarbonate sodium and producing CO2 enhanced the wetting volume of the dosage unit and leads to increasing drug

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diffusion from the superficial area in comparative research utilizing a hydroxypropylmethylcellulose matrix [55]. The carbon dioxide bubbles, on the other hand, impede the diffusion channel, resulting in a reduction in the medication release. Gas production could enhance medication delivery in the next step in the process of drug release, according to the same authors [55].

Raft forming system

To enhance the time of retention, many measures are undertaken to keep the dosage unit in the stomach. The technique that is based on raft forming technology is studied as a promise in making novel oral-drug delivery techniques for medication delivery among the different attempts. For example the management of GIT infections and illnesses, raft forming systems have garnered a lot of attention. One of the technologies that have been examined for medication administration and target durability is the raft forming system, which involves the generation of an effervescent buoyant liquid with the formation of in situ gelling capabilities. Furthermore, the in-situ gel that is generated is stable for about (or more than) 48 hrs., allowing for long-term drug release[56]. The procedure used by the raft-forming system comprises the creation of a raft which is a continuous layer. When a thick adherent gel comes into contact with stomach juices, each piece of the liquid material expands, forming a raft[56]. A layer of gel floats atop the stomach fluid since the bulk density of this layer is lower than the gastric fluid, which is caused by CO2 production [56].

Hydrodynamically balanced systems (HBS)

In a non-fasting state, it found pellets having a relative density of about 0.86 g/ml had prolonged stomach retention than pellets having a relative density of about 1.33 g/ml. Several patents are obtained on various floating-type systems, including tablets, capsules, and multiple-layered tablets, as well as hydrodynamically balanced systems (HBS) [57]. Hydrocolloids are employed in HBS to create a swelling-hydrated border layer that traps air and gives the system its floating qualities. It has been claimed that flotation systems with gaseous materials contained in chambers, or chambers inflate and contain liquids that could create gas at a temperature of the body and stay afloat over gastrointestinal contents [32][43]. Created a sodium bicarbonate-containing alginate matrix capsule that released trapped carbon dioxide in the gel network. [58]. Preparation of a multi-unit floating pill with a core seed sandwiched between two distinct layers. In aqueous media, carbon dioxide can be produced from a layer containing tartaric acid and sodium bicarbonate. A swellable membrane which found in the outer layer and has the gas material, causing the system to float. Within about 10 minutes of wetting in the test field, the system began to float and remained afloat for the next 5 hours [59].

Volatile systems

Fill an inflated chamber with a volatile liquid, like ether or cyclopentane, which volatilizes near body temperature, permitting the chamber to be inflated in the gut [32]. Various types of hydroxypropylmethylcellulose and alginate which are hydrophilic polymers frequently utilized as a matrix in noneffervescent systems because they allow for drug release control [60].

Ion-exchange systems (resin)

GRDDs beads were prepared by covering them with Eudragit-RS partially permeable polymeric membrane, the resin was charged using bicarbonate. Bicarbonate was freed using hydrochloric acid, resulting in carbon dioxide formation. The carbon dioxide became stuck in the inner part of the membrane, which lead to the particle of resin floating [61].

Magnetic Systems

Gröning and colleagues devised a gastroretentive medication delivery device that included a tiny magnet that could be steered by an extracorporal magnet linked to the belly[62]. Inside the stomach, a capsule was successfully delayed, hence boosting the drug's absorption at its precise absorption window and lengthening the gastric residency duration. However, it was discovered that the findings varied depending on whether the patient if he was in a non-fasting or fasting state.

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Clinical trials using three different delivery modalities were carried out. The first method used an extracorporal magnet with a magnetic depot tablet, the second system did not utilize an extracorporal magnet, and the third system used a formulation with an immediate-release pattern. When an extracorporal magnet was utilized, a 12-hour stomach retention time was established, and an improvement in drug absorption related to the magnetic depot pill was shown when measuring plasma-drug concentration. Due to the accuracy with which the magnet must be placed externally, there are problems in patient compliance when using the magnetic system [62].

Expandable type Systems

Expandable systems for drug delivery are designed to have a prolonged GRT by increasing the volume or form of the drug delivery system [63]. For the system to work properly, three general configurations must be considered [2]:

1- Small size for easy ingestion
2- Inside the stomach, expanded form to hinder its passage via the sphincter (pyloric),
3- After complete medication release, the system's size is reduced to allow for evacuation.

This system is referred to as the "pyloric sphincter restriction system" because of its capacity to limit the pyloric sphincter so it's called a "plug-type system." Swelling and unfolding are two techniques of system expansion that permit volume and form adjustment, respectively [64]. The drug is released from such a system and swelling occurs under the principle of diffusion [65]. Polyethylene oxide, HPMC, and carbopol are hydrophilic type polymers used in the formulation to absorb water from the stomach juices and expand the system. Inside the capsules, the polymers and medication may be compressed or folded to produce the unfolding system. Gelatin is dissolved when it comes into touch with stomach juice, releasing the mechanically favored inflated structure [50].

Within a capsule, biodegradable polymers with diverse geometrical forms can be created and crushed. To preserve the dosage form's prolonged release profile, selecting a biodegradable polymer with the appropriate viscosity level, molecular weight and swelling properties are crucial. Several new polymers which are quickly swell when they come into touch with GI fluid[17], [43].

Expandable systems, on the other hand, have several drawbacks, including the inability to store easily hydrolyzable, biodegradable polymers; difficulty in manufacturing and not cost-effective; keeping structural architecture; and the potential for intestinal obstruction, gastropathy, and bowel adhesion [50], [66].

Applications of the GRDDSs in the cardiovascular diseases

Improve drug bioavailability

To test how hydrophobic and hydrophilic retardants affected in vitro drug release, the study's objective has been to construct a gastroretentive floating tab. containing atenolol. Atenolol is known to have a bioavailability of about 50% (which is low) and this low bioavailability is because of its poor absorption from the intestine. Atenolol floating tablets were developed to improve drug bioavailability by increasing stomach retention and extending drug release [67].

The direct compression technique is used to make tablets of the floating type containing Atenolol with different amounts of (HCSO and HPMC)which act as retardants and sodium bicarbonate. The powders of drug and polymers were precisely weighed and a sieve of 40 mesh was sieved. All ingredients composed of drugs and excipients except magnesium stearate were combined and mixed for about 15 minutes together. After the medication and other components had been thoroughly mixed, a lubricant(magnesium stearate) is added, and the mixture is thoroughly blended for about 2-3 minutes. A single punch machine for tablet compression is used with 10mm round flat punches, the mixture is compressed to form tablets with about 300 mg average weight[67].

The purpose of this type of research is to create the best (GRDDS) for the Losartan administration[46]. At various compression pressures, floatable and swellable GRDDS pills

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containing different polymers (sodium carboxymethyl cellulose, hydroxyethyl cellulose (HEC), and sodium bicarbonate) are made to evaluate swelling properties and floating capability. Losartan release rates from these tablets were pH-dependent. The bioavailability of system A which contain (Losartan 8.33 %, sodium bicarbonate 3.33 %, and HEC 91.67%) is around 164 % in comparison to immediate release form in clinical trials [46].

Prolong/controlled release of drug

The goal of like study was to create a carvedilol gastro-retentive controlled release mechanism employing the biological macromolecule chitosan. For the standardization of tripolyphosphate and remedial time, a complete factorial design was used. The study's findings suggested that a possible medication carrier for carvedilol with better bioavailability could be a gastro-retentive controlled release system made using chitosan. [68].

For a long time, developing a captopril formulation with a regulated release has been a challenge. A floating tablet of captopril containing Metolose and sodium bicarbonate to give a sustained release effect was investigated in vitro, with the quantities of Metolose and bicarbonate being varied. In comparison to the same preparation containing sodium bicarbonate, the release patterns of a preparation containing captopril with Metolose matrix show a higher medication release. This is due to carbon dioxide bubbles obstructing the diffusion route [55].

Approximately 14% of a losartan therapeutic dose is converted into an active metabolite, which has an approximate half-life of 6-9 hours but is about 10-40 fold more power than the parent compound. Losartan is quickly absorbed after oral administration. Losartan has limited bioavailability because it has different first-pass metabolism and insufficient absorption. Work to develop a formula have floating and swelling properties using a mixture of hydroxyethylcellulose, sodium bicarbonate, and chitosan to minimize buoyancy lag time and improve buoyancy time while maintaining a consistent release of the drug [66].

Reducing dosage frequency (increasing half-life)

A controlled release delivery system that relies on microsphere preparation of polyglycerol esters of fatty acids was used to administer the antihypertensive medicine delapril hydrochloride. By selecting polyglycerol esters of fatty acids with the proper hydrophilic-lipophilic balance (HLB) for the medium, the in vitro release study was controlled. Orally injected into rats the microspheres released about 80% of the medication in a round of 6 hours. In comparison to the administration of a solution, after taking the microsphere the concentration of the active metabolite in plasma was preserved. In vivo release profile matched the in-vitro release profile closely. A pharmacological impact of this antihypertensive drug on angiotensin-I (which causes an increase in the pressure) was sustained when the microsphere was delivered, demonstrating concordance with the curve of plasma versus concentration [69].

Improving drug solubility

Employing response surface methodology, create and improve floating tablets containing carvedilol cocrystals that float in the gastric fluids of the stomach with a decreased buoyancy lag time and regulated drug release. The improved formulation's releasing, floating, and swelling properties were tested. As a result, a tablet with floating properties containing carvedilol cocrystals was developed by using design of experiment (DOE) approaches to improve its solubility [70].

Drug exhibit window absorption

Diltiazem hydrochloride is commonly employed in hypertension and angina pectoris treatment, acting by blocking the calcium channel. Diltiazem has low bioavailability of about 30 to 40% because it undergoes first-pass metabolism. This drug has an absorption zone in the upper small intestine, which results in inadequate drug absorption and quicker drug clearance, resulting in suboptimal plasma drug levels. Because standard CR formulations failed to provide the necessary drug release profile inside the absorption window, Diltiazem was developed as

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a unique gastroretentive drug delivery technology [71]. Other examples are shown in Table 3.

TABLE 3: Examples of Application of GRDDs in the Cardiovascular System

Drug	Type of GRDDs	Formula's target	Reference
Propranolol	Floating system	Low bioavailability	[72]
Atorvastatin	Floating system	Low bioavailability	[73]
Furosemide	Low-density floating system	Narrow absorption window	[74]
Captopril	Floating matrix tablet	Short half-life	[55]
Metoprolol	A swellable and floating system	Exhibit window absorption with a short half-life	[75]
Verapamil	Floating pellet	Low solubility in alkaline pH	[76]
Atenolol	Bilayer matrix tablet	Poor absorption from the intestine	[77]
Clopidogrel	High-density multiparticulate pulsatile tablet	Narrow absorption window	[78]

Natural products formulated as GRDDs for the management of cardiovascular problems

The main cause of death worldwide is cardiovascular diseases (CVDs), mostly in low and middle-income populations, Currently, active ingredients in herbal medications are widely used to treat CVD, such as coronary heart disease and hypertension [79], [80]. Examples of natural products formulated as gastroretentive delivery systems and other types of delivery are founded in Table 4.

TABLE 4: Natural Products such as GRDDs and Other Delivery Systems

Natural products	**Delivery systems**	**Uses**	**References**
Ginsenoside Rb1	Chitosan-Alginate-Lovastatin composite films	Coronary heart disease, Ischemia-reperfusion injury	[81]
Matrine	Chitosan-alginate gastric floating beads	Arrhythmia Coronary heart disease Acute myocardial infarction	[82]
Polyphenols	Floating sustained release system	Enhancement of endothelial function, Reduction of cardiovascular diseases	[83]
Anthocyanin	Floating alginate microspheres systems	Diabetes	[84], [85]
Paeonol	Floating system	Coronary heart disease Gastric ulcer	[80], [86]
Hesperidin	Sodium alginate beads integrated with a self-micro-emulsifying drug delivery system	Ischemia-reperfusion	[80], [87]
Curcumin	Raft forming systems	Hypertension and gastric ulcer	[80], [88]

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Ligusticum chuanxiong	Microsphere sustained release	Heart failure, coronary heart disease, and hepatoprotection	[80], [89]
Anthocyanins	In-situ gel (alginate based)	Diabetes type-2	[90]
Tanshinone IIA	Chitosan-based microsphere	Cardiovascular diseases	[91]
Curcumin	Floating in-situ gel system	Antioxidants (various cardiovascular diseases)	[92]

Natural products prepared as gastro retentive for treating various diseases (other than cardiovascular diseases)

From ancient times to the present, herbal medications, and plants of medicinal importance, that produce natural products have been utilized to cure a variety of disorders; there is growing attention has been placed on natural products, and many medicinal plants and herbal remedies[93].

TABLE 5: A Summary of Natural Products Prepared as Gastroretentive Systems

Natural products	Delivery systems	Uses	References
Berberine	Floating system	Gastric ulcer	[94]
Panax notoginseng	Alginate microsphere	Alcoholic gastric ulcer	[95]
Silymarin	Floating microsphere	Hepatoprotection	[96]
quercetin	Raft forming system	Gastric ulcer	[97]
Berberine	Floating tablet	Gastric ulcer	[98]

Current medication manufactured by gastroretentive technology

Many companies adopted GRDDs technologies to manufacture drugs with a new delivery system, a summary of these drugs and their manufacturing companies can be found in Table.6

TABLE 6: Current medication manufactured by gastroretentive technology [1], [4], [24], [99]

Drug(s)	Product name	Pharmaceutical company	GRDDs technology
Rifaximin	Xifaxan®	Lupin, India	Bioadhesive tablets
Ofloxacin	Zanocin® OD	Ranbaxy, India	Effervescent floating system
Metformin hydrochloride	Riomet® OD	Ranbaxy, India	Effervescent floating system
Ferrous sulfate	Conviron®	Ranbaxy, India	A floating system with gel-forming preparation
Ciprofloxacin	Cifran® OD	Ranbaxy, India	Floating (effervescent) system
Prazosin hydrochloride	Prazopress® XL	Sun Pharma, Japan	Swelling and floating system(effervescent type)
Gabapentin	Gabapentin® GR	Depomed, Inc., USA	Swellable polymers technology: AcuForm™
Ciprofloxacin	ProQuin® XR	Depomed, Inc., USA	Swellable polymers technology: AcuForm™
Metformin hydrochloride	Glumetza®	Depomed, Inc., USA	Swellable polymers technology: AcuForm™

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Simethicone	Non-Ace® Tablets	Sato Pharma, Japan	Foam-based floating system
Metformin hydrochloride	Metformin® hydrochloride	Galenix, France	Minextab Floating® system
Cefaclor	Cafeclor® LP	Galenix, France	Minextab Floating® system
Tramadol	Tramadol® LP	Galenix, France	Minextab Floating® system
Levodopa and benserazide	Madopar®	GlaxoSmithKline Roche, UK	Gastroretention with osmotic system Floating, CR capsule
Diazepam	Valrelease®	GlaxoSmithKline Roche, UK	Gastroretention with osmotic system Floating, CR capsule
Carvedilol	Coreg® CR	GlaxoSmithKline Roche, UK	Gastroretention with osmotic system Floating, CR capsule
Alginic acid and sodium bicarbonate	Liquid Gaviscon®	Reckitt Benckiser Healthcare, UK	A floating system with alginate effervescent liquid
Aluminum magnesium antacid	Topalkan®	Pierre Fabre Medicament, France	Floating alginate liquid
Misoprostol (100/200 μg)	Cytotec®	Pharmacia Ltd., UK	Bilayer floating capsule

Patency and future prospective in GRDDSs

As we mentioned in the literature, gastroretentive technologies are considered to be a recent and advanced manner for the formulation of dosage forms. Although the requirements for designing GRDDs need more effort and a more complicated technique compared with a classical tablet, many patents are reported and marketed to the market to reach the most efficacious formula and effective gastroretentive systems [100].

The approach for achieving effective GRDD dosage form may be diverse depending upon the drug, polymers, and the problem that has to be overcome by fabrication drug in the form of gastro retention. While some dosage forms are prepared to have a single mechanism, others are prepared to have combined mechanisms like floating and mucoadhesion[101]. Also, more recently polymers having shape memory properties are being investigated in the preparation of the GRDDs, the author found great advantages to using such a method and recommended more improvements to modify the drug release[10]. Novel and advanced methods are utilized in the preparation of gastroretentive systems, for example using the gastric retention technique, which could enhance the bioavailability of poorly water-soluble drugs and get patency for their work[102]. Many formulations maybe give good results in vitro studies but still can not be fabricated as dosage forms due to many parameters that should be given attention in the preparation of gastroretentive systems, so patency in this advanced technology needs more monitoring for several parameters[9]. According to the mentioned information, patency in GRDDs technologies is challenging and required special care for many parameters and knowledge of stomach anatomy and physiology.

TABLE 7: A List of Patency in Gastroretentive System for Drug Delivery [103]

Type of the gastroretentive system	Year	Patent Number
Powder formulation has floating properties	1992	US 5769638
Delivery devise with self-retaining in GIT	1993	US 5198229
Bilayer floating dosage form	1993	US 5232704
Buoyant system for oral therapy	1997	US 5626876
Gastro-retentive microspheres	2001	US 6207197
Programmatic floating technology	2012	US 8277843

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GR extended release composition of the therapeutic agent	2014	US 8808669
Floating GR dosage form	2016	US 9314430
Controlled-release floating pharmaceutical compositions	2017	US 9561179
The gastro retentive liquid dosage form	2003	US 6635281
Gastric retaining system with multiple layers	2004	US 6797283
GRDDS comprises an extruding hydratable polymer	2013	US 8586083
Doxycycline gastro retentive system	2015	US 9119793
Carbidopa gastro retentive system	2015	US 20150366832
Osmotic buoyant tablets	2015	US 20150231084
GR pills of pregabalin	2016	US 20160338949
Pharmaceutical controlled release composition with bioadhesive properties	1995	US 5472704
Mucoadhesive for CR of the active principle	1999	US 5900247
Bioadhesive dosage form	2001	US 6303147
Mucoadhesive oral granules of carbomer polymer	2001	US 6306789
A pharmaceutical system for the GI delivery system of drug	2015	US 8974825
Gastric retaining drug delivery device for controlled delivery of drugs	1988	US 4767627
Pharmaceutical tablet exhibiting high volume increase when gets in contact with gastric fluids	1998	US 5780057
Gastro-retentive, an oral dosage form for CR of sparingly soluble drugs	1999	US 5972389
Prolonged-release drug delivery device adapted for gastric retention	2003	US 6548083
Dosage form prolongs the duration of release of drug in the gastric region during a non-fasting state	2003	US 6635280
Mixtures of polymer for gastric retention tablets	2004	US 6723340
Expandable gastro retentive system for increased gastric retention time	2004	US 6776999
Gastro-retentive dosage form with the limited release of the drug in lower GIT	2011	US 7976870
Gastroretentive tablet	2016	US9393205
Extended-release acamprostate (gastroretentive dosage form)	2017	US9801816
Raft system in the stomach	2001	US 0119994
Pectin in situ gel system	2002	US 0063980

CONCLUSION

Recently, there has been a lot of research into the delivery of the drug via gastroretentive technologies. these technologies present methods for increasing drug bioavailability and delivering medications having a narrow absorption window under strict control. The gastroretentive systems do not just deliver a regulated release of the medication, but they also deliver it to the areas where its absorption is greatest. The development of GRDD dosage forms is challenging because such dosage forms will stay in the stomach for a prolonged time, resulting in continuous absorption of the medium into these dosage forms, which may alter the density of GR dosage forms. An area of promising work by using dual technologies like floating and mucoadhesive systems or expandable and buoyant systems is now extensively studied, and other forms like magnetic systems are under research now to reach a more reliable form in the concept of synthesis and absorption. The GR are used recently in cardiovascular drugs to enhance many pharmaceutical factors like solubility and half-life and improve drug bioavailability, also these systems are used to manufacture controlled-release cardiovascular medications. Many types

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of research are focusing on herbal medicine and medicinal plants in the treatment of a variety of diseases especially cardiovascular diseases, we mentioned different medicinal plants that are used in treating cardiovascular problems and formulated as GR dosage forms to improve their properties like bioavailability, absorption, and half-life. Further studies and research need to be conducted in this very promising and developing field.

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Author's contribution

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