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Facts and Features of Gastroretentive Drug Delivery System

Krishnagiri Krishnababu[1*], Gururaj S Kulkarni[2], Padmaa M Paarakh[3]

[1,2]Department of Pharmaceutics, the Oxford College of Pharmacy, Bengaluru, India.*
[3]Department of Pharmacognosy, the Oxford College of Pharmacy, Bengaluru, India.

Corresponding Email: [1]k.krishnababu2020@gmail.com*

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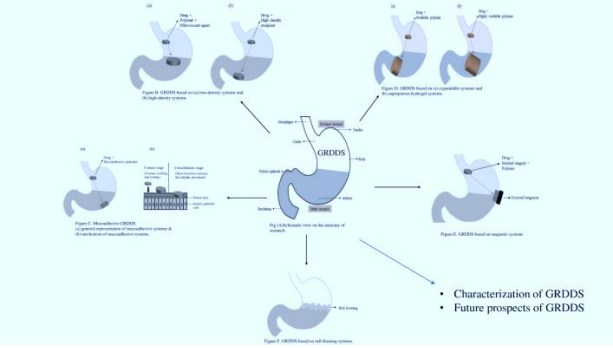
Abstract: ***Oral drug delivery has gained a lot of popularity because of patient compliance and the simplicity of administration. It only provides a small number of benefits for medications with poor bioavailability because of inadequate digestion and absorption in the latter stages of the GI tract. In this scenario, GRDDS have emerged as a preferred choice for drug administration with unique qualities such as a narrow absorption window, avoiding metabolism, instability in high alkaline pH, and improved solubility in low pH. In this present review, we discuss the Merits and demerits, the physiology of the stomach, and factors affecting the grdds. Various gastrointestinal technologies, including floating, non-floating, expandable, superporous hydrogel; Bioadhesive, magnetic, and raft system, as well as their applications, is outlined. In addition, potential future developments on this technology to minimise stomach emptying rate in both fasting and fed stages are highlighted. In the end, this review might assist formulation scientists and researchers in designing the GRDDS.***

Keywords: Gastroretentive Drug Delivery System, Floating, Effervescent, Characterisation, Patents Etc.

Graphical Abstract



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1. INTRODUCTION

In contrast to more conventional routes like intravenous infusions and intramuscular injections, oral delivery is the preferred method for drug administration because it is more natural and less invasive. This, in turn, increases patient compliance and improves safety compared with other methods. [1] Because conventional dosage forms only stay in the stomach for a short period of time (0.5-2 hours) before moving on to the small intestine, where they are absorbed in 3-6 hours, it is challenging to regulate the drug's release delay and prolonged stomach retention.

Gastroretentive DDSs (GRDDS) are a class of DDSs that are designed to improve the bioavailability of drugs by prolonging their residence time in the stomach. The main idea behind GRDDS is to keep the drugs in the stomach for an extended period, allowing them to be slowly released and absorbed. GRDDS have the potential to enhance the therapeutic efficacy of a variety of drugs, including those that have poor solubility or low permeability, and those that are rapidly metabolized later parts of the body or eliminated from the body. [2] With the introduction of a variety of controlled delivery systems, the inconvenience of conventional tablets or capsules, which resulted in a transient overdose, followed by a long period of underdosing, was overcome.

Some drugs are absorbed in a particular portion of the GIT only or are absorbed to a different extent in various segments of the GIT. Such drugs are said to have an absorption window, which identifies the drug's primary region of absorption in the GIT.[3] An absorption window exists because of physiological, physicochemical, or biochemical factors. The pH-dependent solubility and stability level of a drug plays an important role in its absorption. A drug must be in a solubilized and stable form to successfully cross the biological membrane, and it will experience a pH range from 1 to 8 as it travels through the GIT.[4] The average time required for a dosage unit to traverse the GIT is 3-4 hrs, although slight variations exist among various dosage forms.

Criteria for Selection of Candidate Drugs for GRDDS
GRDDS are designed to increase the duration of medication stays in the stomach, which can be particularly beneficial for drugs that have a narrow absorption window in the upper GI tract. The criteria for selecting candidate drugs for GRDDS can include:

Solubility and Stability: The drug should be sufficiently soluble in the stomach and should not degrade in the acidic environment.

Absorption Site: The drug should have its absorption site in the stomach or initial part of the small intestine to achieve a therapeutic effect.

Low Absorption Rate: Drugs with low bioavailability and low absorption rates in the small intestine, such as some peptides and proteins, may be good candidates for GRDDS.

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Short Half-Life: Drugs with a short half-life may benefit from the sustained release properties of GRDDS.

High Dose Requirement: Drugs that require a high dose to achieve therapeutic efficacy may be good candidates for GRDDS, as sustained release formulations can help maintain therapeutic drug levels in the body.

Narrow Therapeutic Window: Drugs with a narrow therapeutic window, where small changes in dosage can result in significant changes in efficacy or toxicity, may benefit from the controlled release properties of GRDDS.

Patient Compliance: Drugs that require frequent dosing may benefit from the extended-release properties of GRDDS, which can improve patient compliance. The selection of candidate drugs for GRDDS should be based on a thorough understanding of the drug's physicochemical properties, pharmacokinetics, and therapeutic requirements.

Basic Anatomy and Physiology of GIT

The stomach is a muscular sac-like structure in the upper belly that aids in food digestion. It is characterized into four major areas, each having its own anatomical and functional characteristics: the cardia, fundus, body, and antrum. The stomach has a capacity of 1.5 litres on average and may grow to handle bigger meals. The stomach has a very acidic environment with a pH of roughly 2, which is maintained by the release of hydrochloric acid by the parietal cells of the gastric mucosa. This acidic environment is necessary for protein digestion because it stimulates pepsin, an enzyme that breaks proteins down into smaller peptides. The stomach also secretes mucus, which protects gastric mucosa from the corrosive effects of gastric acid. The stomach has a complex musculature and it is consisting of an inner circular layer and an outer layer of longitudinal smooth muscle. The rhythmic contractions of these muscles, known as peristalsis, mix and propel food through the stomach, ultimately delivering to the small intestine for digestion and absorption. The antrum region of the stomach is particularly important for the regulation of peristalsis, as it contains pacemaker cells that coordinate the contractions of the smooth muscle. The stomach is also involved in the regulation of appetite and satiety. The release of various hormones, such as ghrelin, stimulates hunger and promotes food intake, while the release of other hormones, such as cholecystokinin, signals the brain to reduce appetite and terminate food intake.

Physiology of Gastrointestinal Tract

Fasting and fed states both have gastric emptying. The motility pattern, however, differs between the two phases. During the fasting state, an interdigestive series of electrical events occur, which cycle through the stomach and intestine every 2-3 hours. This is known as the interdigestive myloelectric cycle (IDMC) or migrating myloelectric cycle (MMC), and it is broken into four stages.

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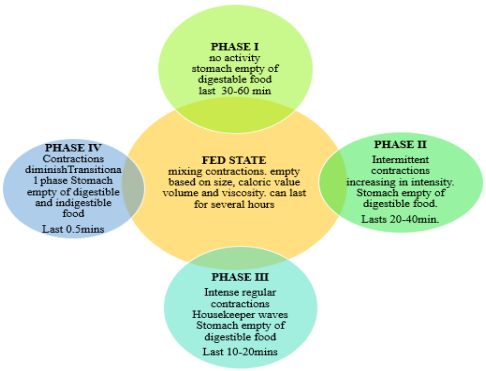

Figure.1 Phases involved in gastric emptying.

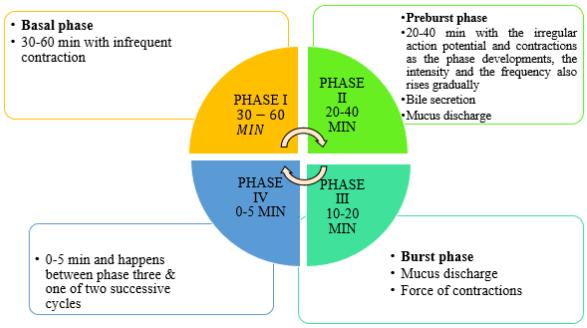

Figure.2 Phases of gastric cycle

Table 1: An overview of anatomical and physiological differences among the various segments of gastrointestinal tact

S.NO	Section	Average length (cm)	Diameter (cm)	Absorption mechanism	pH	Major constituents	Transit time of food (h)
1.	Oral cavity	18	10	PD, CT	5.2-6.8	Amylase, maltase, ptyalin, mucins	Short
2.	Oesophagus	25	2.5	-	5-6	-	Very Short
3.	Stomach	20	15	PD, CT	1.2-3.5	HCL, renin, pepsin, lipase, castle's intrinsic factor	0.25-3.00
4.	Duodenum	25	5	PD, CT, AT, FT, IP	4.6-6.0	Bile, amylase, CYP3A4, maltose, lipase, nuclease	1.0-2.0
5.	Jejunum	300	5	PD, CT, AT, FT	6.3-7.3	Amylase, lactase, maltase, CYP3A5, sucrase	-
6.	Ileum	300	2.5-5.0	PD, CT, AT, FT, IP, P	7.6	Lipase, enterokinase, nuclease, nucleotidase	1.0-10.0
7.	Cecum	20	2.5-5.0	PD, CT, AT, P	7.5-8.0	-	Short
8.	Colon	150	5	PD, CT	7.9-8.0	-	4.0-4.5
9.	Rectum	17	2.5	PD, CT, P	7.5-8.0	-	Inconsistent

PD; passive diffusion, CT; convective transport, AT; active transport, FT; facilitated transport, IP; ion pair, P; pinocytosis

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Gastric Emptying

Gastric emptying is a process by which the stomach releases its contents into the small intestine for further digestion and absorption. It is a complex process that is regulated by several factors, including the type and quantity of food ingested, the presence of hormones and neural signals, and the condition of the gastrointestinal tract. The rate of gastric emptying is influenced by the composition of the food ingested. For example, liquids and small particle sizes are usually emptied more quickly than solid foods and large particles. The presence of fat, fiber, and protein in the food can also slow down gastric emptying, as these nutrients require more time for digestion and absorption. Hormones and neural signals also play a role in regulating gastric emptying. The release of certain hormones, such as cholecystokinin (CCK) and glucagon-like peptide 1 (GLP-1), can slow down gastric emptying and promote satiety. Similarly, neural signals from the gastrointestinal tract, such as the enteric nervous system and the vagus nerve, can also influence gastric motility and emptying. Gastric emptying can be affected by certain gastrointestinal conditions, such as gastroparesis, a condition in which the stomach empties too slowly.

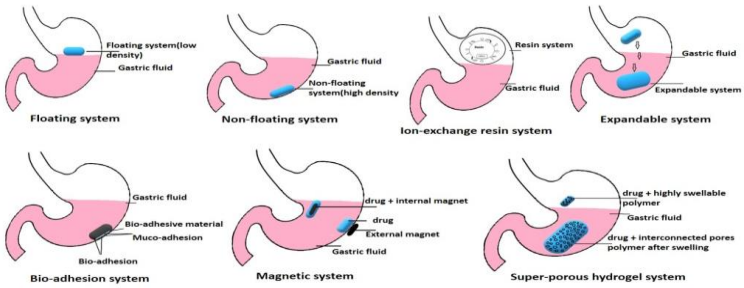

Fig. 3 Approaches to Gastroretentive drug delivery system

Current Approaches to Gastroretentive Drug Delivery System

A. Floating DDSs [9]

FDDS are a type of GRDDS that are designed to remain buoyant in the stomach and release the drug slowly over time. These systems can be formulated as tablets, capsules, or multiparticulate dosage forms such as microspheres or pellets. FDDS are typically composed of a low-density matrix or coating that incorporates gas-generating agents or hydrocolloids to enable the system to float on the gastric contents. The release rate of the drug is controlled by the diffusion of the drug from the matrix or the erosion of the matrix itself. The main advantage of FDDS is their ability to prolong gastric residence time, which in turn leads to improved drug absorption, increased bioavailability, and reduced dosing frequency. The prolonged gastric residence time of FDDS allows for drug absorption in the upper gastrointestinal tract, leading to higher drug concentrations and improved bioavailability. The controlled drug release provided by FDDS can also reduce the frequency of drug administration, leading to improved patient compliance. There are different types of FDDS, including single-layer floating tablets, multilayer floating tablets, and floating multiparticulate dosage forms such as microspheres or pellets. Single-layer floating tablets are typically composed of low-density polymers or hydrocolloids, such as HPMC or xanthan gum, and gas-generating agents, such as sodium bicarbonate or citric acid. Upon contact with gastric fluid, the gas-generating agents react and produce carbon dioxide bubbles, which

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enable the tablet to float on the gastric contents. The drug is then released slowly from the matrix by diffusion or erosion. Multilayer floating tablets are composed of multiple layers, each with a different composition, and are designed to provide controlled release of the drug. The outer layer of the tablet is typically composed of low-density polymers or hydrocolloids that enable the tablet to float, while the inner layer contains the drug and is designed to provide sustained release. The release rate of the drug is controlled by the rate of diffusion through the outer layer and the rate of erosion of the inner layer. Floating multiparticulate dosage forms, such as microspheres or pellets, are composed of small particles that are designed to remain buoyant in the stomach and release the drug slowly over time. The particles can be coated with low-density polymers or hydrocolloids that enable them to float on the gastric contents. The release rate of the drug from the particles is controlled by the diffusion of the drug through the coating or the erosion of the coating itself.

B. Mucoadhesive DDS

Mucoadhesive DDSs are a type of DDS that utilizes the property of mucoadhesion to prolong the residence time of the drug at the site of administration. Mucoadhesion is the ability of a material to adhere to the mucosal surface of biological tissues, such as the gastrointestinal tract, nasal cavity, or ocular surface. The mucoadhesive properties of a material are influenced by various factors, including surface chemistry, surface energy, and charge. Mucoadhesive DDSs have several advantages over conventional DDSs, including improved drug bioavailability, reduced dosing frequency, and improved patient compliance. By prolonging the residence time of the drug at the site of administration, mucoadhesive DDSs can improve drug absorption and bioavailability. The controlled drug release provided by these systems can also reduce the frequency of drug administration, leading to improved patient compliance. There are different types of mucoadhesive DDSs, including tablets, patches, gels, and microspheres. Mucoadhesive tablets are typically composed of polymers, such as chitosan, sodium alginate, or polyacrylic acid, that adhere to the mucosal surface of the gastrointestinal tract. The release rate of the drug from the tablet is controlled by the rate of diffusion through the polymer matrix or the erosion of the matrix itself.

C. High-Density Ddss

HDDS are a type of GRDDS that utilizes high-density materials to provide sustained and localized drug delivery. HDDS can be implanted into the body or delivered through a catheter or injection and are designed to release the drug for an extended period. This type of DDS is particularly useful for treating chronic conditions that require long-term drug therapy. A high-density material, such as barium sulfate, tungsten, or platinum, is typically combined with the drug and formed into a solid or semi-solid matrix. The high-density material provides a radiopaque marker that allows the physician to track the location of the DDS within the body.[22,23] The drug is released from the matrix over time, providing a sustained and localized therapeutic effect. There are several advantages of using HDDS for drug delivery. First, HDDS can provide a sustained drug release over a prolonged period, reducing the frequency of drug administration and improving patient compliance. Second, HDDS can provide localized drug delivery to a specific site, reducing the risk of systemic side effects. Third, the radiopaque marker allows the physician to monitor the location and position of the DDS within the body, ensuring accurate and precise drug delivery.

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D. Superporous Hydrogel Ddss

Superporous hydrogels (SPH) are a type of hydrogel that have the ability to absorb and retain large volumes of water, which results in a highly swollen network structure. This unique property of SPH has led to their use in drug delivery applications, where they offer several advantages over traditional DDSs. SPH DDSs are highly porous, which allows for the incorporation of large amounts of drugs. The high porosity also enables rapid drug release and promotes diffusion of the drug molecules, leading to faster drug absorption. SPH can be formulated to be pH-sensitive or temperature-sensitive, which allows for targeted drug delivery to specific locations within the body.

E. Magnetic DDSs

Magnetic DDSs (MDDS) are a type of drug delivery technology that utilizes magnetic fields to control the release and targeting of drugs. MDDS have the potential to improve drug efficacy and minimize side effects by directing the drug to the specific site of action. The MDDS system consists of three main components: magnetic nanoparticles, drug molecules, and an external magnetic field. Magnetic nanoparticles are small particles that are typically composed of iron oxide and are coated with a biocompatible material. The drug molecules are attached to the surface of the magnetic nanoparticles. The external magnetic field is used to manipulate the movement of the magnetic nanoparticles and guide them to the target site.

Magnetic DDSs can be divided into two categories:

1. Passive targeting
2. Active targeting

Passive targeting involves the use of a magnetic field to target a specific area of the body. [5] The magnetic nanoparticles are injected into the bloodstream and then directed to the target site using a magnetic field. Active targeting involves the use of specific ligands that bind to receptors on the target site. The magnetic nanoparticles are coated with these ligands and are then directed to the target site using a magnetic field. MDDS offer several advantages over traditional DDSs. The targeted drug delivery minimizes the drug exposure to healthy tissues and reduces systemic toxicity. MDDS can also be used to deliver drugs to the brain, which is typically difficult to achieve with traditional drug delivery methods due to the blood-brain barrier. Magnetic DDSs have been used to deliver a wide range of drugs, including anticancer drugs, antibiotics, and genes. Magnetic nanoparticles have also been used as contrast agents for magnetic resonance imaging (MRI).

F. Raft Forming System [10]

The raft forming system is a type of GRDDS that is designed to improve the bioavailability of drugs that are absorbed in the upper gastrointestinal (GI) tract. The system is composed of a mixture of antacids and polymers that form a gel-like layer on the surface of the gastric contents, creating a floating raft that adheres to the gastric mucosa and prolongs the gastric residence time. Aluminum and magnesium hydroxides, which neutralize gastric acid and raise the pH of the stomach, are commonly used in the raft forming system. This increased pH creates an environment that is more conducive to the absorption of weakly acidic drugs, which are typically absorbed in the upper GI tract. The polymers used in the raft forming system are typically mucoadhesive and create a gel-like layer on the surface of the gastric

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contents, which adheres to the gastric mucosa and prolongs the gastric residence time. The most used polymers in the raft forming system are sodium alginate, pectin, and carbomer. The mechanism of action of the raft forming system is based on the formation of a floating raft on the surface of the gastric contents, which adheres to the gastric mucosa and prolongs the gastric residence time.[23] The floating raft acts as a barrier that protects the drug from the acidic environment of the stomach, and also slows down the gastric emptying rate, thus increasing the time available for drug absorption.

G. Swellable DDSs

These are also called "plug type systems". These systems are composed of hydrophilic polymers that absorb water and swell in the presence of gastric fluids, thus preventing them from passing through the pylorus and prolonging the gastric residence time. The mechanism of action of swellable DDSs is based on the swelling properties of the hydrophilic polymers used in the system. When the system is administered orally, it absorbs water and swells to a large size, thus preventing it from passing through the pylorus and prolonging the gastric residence time. The degree of swelling of the system is dependent on the properties of the hydrophilic polymer used, including its molecular weight, degree of cross-linking, and pH sensitivity.

H Expandable Gastroretentive Dosage Forms

The expandable gastroretentive dosage forms are typically based on three configurations: a small ('collapsed') form that enables convenient oral intake; an enlarged form achieved in the stomach, preventing passage through the pyloric sphincter; and a final tiny form achieved in the stomach when retention is no longer necessary, i.e. after the gastroretentive dosage forms has released its active ingredient, permitting evacuation.[48,49] Swelling or unfolding in the stomach can cause the stomach to expand. To obtain prolonged configuration, the carrier is dissolved in the stomach, and the gastroretentive dosage forms unfurl or expand out.[50,51]

Table: 4 Few Gastroretentive products available in the market

Product name	Active Ingredient	Technology	Company
Zanócin OD	Oflóxacin	floating system with Effervescence	Ranbaxy
Riómet OD	Metfórmin HCl	floating system with Effervescence	Ranbaxy
Cifràn OD	Ciprófloxacin	floating system with Effervescence	Ranbaxy
Inon Acè tablet	Simethicóne	floating system with Effervescence	Sato Pharma
Gàbapentin GR	Gabàpentin	Polymer-based swelling technology: AcuForm™	Depomed
Prazoprèss XL	Prazósin HCl	Effervescent and swelling-based floating system	Sun Pharma
Cipró XR	Ciproflóxacin HCl and Betaine	Erodible matrix based system	Bayer
Baclófen GRS	Baclófen	Coated multi-layer floating and swelling system	Sun Pharma
Liquid gaviscón	Alginic acid and Sódium bicarbonate	Effervescent floating preparation containing sodium alginate	Reckitt Benckiser
Xifaxàn	Rifaximîn	Bioadhesive Tablets	Lupin
Convirón	Ferróus Sulphate	floating system forming Colloidal gelatinous layer	Ranbaxy

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Fig. 5 Few Patents for some Gastroretentive drug delivery system

Patent/ Application no.	Disclosure
US 8,012,496 Sun Pharmaceutical	This patent discloses a stomachal retention-controlled drug delivery system comprising: (a) a controlled unleash core comprising a drug, a extremely swellable compound and a gas generating agent, aforementioned core being capable of swelling and achieving flotation apace whereas maintaining its phys. integrity induct fluids for prolonged periods, and (b) a apace emotional coat composition comprising a similar drug as within the core and pharmaceutically acceptable excipients, whereby the coating composition surrounds the core such the system provides a biphasic unleash of the drug in duct fluids. The gastric retention controlled-release tablets were obtained by mixing baclofen 20.0 mg, lactose 30.0 mg, hydroxyethyl cellulose 400.0 mg, sodium starch glycolate 150.0 mg, $NaHCO_3$ 40.0 mg, and hydroxypropyl Me cellulose 136.0 mg, granulating the mixture with silicified microcryst. cellulose 90.0 mg, talc 24.0 mg, polyethylene glycol 10.0 mg, and hydroxypropyl Me cellulose 100.0 mg to prep. a core, and coating the core with a mixture containing baclofen 10.0 mg and hydroxypropyl Me cellulose 45.0 mg. Tablets prepared achieved flotation in about 10 min.
US 20080107732 Sun Pharmaceutical	This patent application provides a novel gastric retention system in the form of a tablet or a capsule coated with an expandable coating, more particularly, with an expandable coating comprising a film-forming polymer and an expandable component. The gastric retention system is used for controlling appetite and thereforeobesity. A gastric retention drug delivery system was prepared containing 750mg metformin hydrochloride per coated tablets. More than 95% of the tablets were dissolved in pH = 3.0, and 4.5.
IN 2010MU00300 Sun Pharmaceutical	The present invention provides an internal organ retention controlled drug delivery system comprising: (a) a controlled unharness core comprising a drug, an extremely swellable compound and a gas generating agent, (b) a speedily cathartic coat composition comprising constant drug as within the core and pharmaceutically acceptable excipients. A internal organ retention controlled drug delivery system contained, lactose, hydroxyethyl cellulose, sodiumstarch glycolate,sodiumbicarbonate, hydroxypropyl methylcellulose, extragranular silicified microcryst. cellulose, talc, polyethylene glycol, hydroxypropyl methylcellulose in the core, and baclofen, hydroxypropyl methyicellulose in the coat.

Future Prospectives of Grdds

Gastroretentive drug delivery systems (GRDDS) have received a lot of attention in the pharmaceutical industry, especially for medications that are absorbed from the upper section of the intestine. These systems provide promising alternatives for circumventing the limits of traditional dosage formats. [53] While several GRDDS technologies have been investigated, each has its own set of constraints. Addressing the problems associated with gastroretention variations, particularly in the fed and fasted stages, remains a top priority for formulation scientists. Combining diverse processes, such as expandable and effervescent floating systems or mucoadhesive and floating systems, could be advantageous in minimising variability and ensuring delayed stomach emptying. [54] Understanding the physicochemical qualities of medications and excipients, as well as the effects of formulation and process variables, is also critical for designing successful GRDDS. The quality by design (QBD) technique can provide useful insights into optimising critical GRDDS quality features. Although magnetic systems show promise, additional clinical research is needed to investigate their clinical applications in humans. Furthermore, advances in imaging technologies, including radiography, scintigraphy, and magnetic marker monitoring, provide non-invasive approaches to analysing the behaviour of dose forms in the stomach and forecasting gastric emptying time. [55]

2. CONCLUSION

Over the last few decades, gastroretentive drug delivery systems (GRDDS) have evolved as an important area of pharmaceutical research and development. These methods provide specific benefits such as customised drug distribution, extended release kinetics, and precise

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control over drug release from a variety of gastroretentive dosage forms. GRDDS have the potential to improve patient compliance and reduce the occurrence of side effects associated with frequent dosing by enabling site-specific drug delivery and maintaining therapeutic drug levels over time. As a result, pharmaceutical companies are expected to progressively adopt and investigate the possibilities of gastroretentive drug delivery technology in the future, resulting in considerable benefits in terms of patent extension and enhanced outcomes for their marketed formulations.

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