RESEARCH PAPER

Conquering Gastric Transit: A Comprehensive Review of Gastroretentive Drug Delivery Systems - From Mechanistic Foundations to AI-Driven Innovations

Tanya Sharma[1], N.G. Raghavendra Rao[2], Pragati Gupta[3], Shivanshu Sharma[4], Anuj Pathak[5*]

[1,3,5] KIET School of Pharmacy, Krishna Institute of Engineering & Technology (KIET), Ghaziabad, Delhi-NCR, Uttar Pradesh, India.

[2] Parul Institute of Pharmacy, Parul University, P.O. Limda, Tal, Waghodia, Dist. Vadodhara - 391 760, Gujarat, India.

[4] School of Pharmacy, Sharda University, Knowledge Park-III, Greater Noida, Uttar Pradesh - 201310, India.

[*] Corresponding Author: Anuj Pathak. Email: anuj.pathak1@gmail.com

ABSTRACT

GRDDS is an advanced drug delivery system that overcomes the challenges shown by oral drug delivery systems. The GIT shows various physiological and inter-patient variability that led to the development of GRDDS to make an effective dosage form. This approach is useful for drugs having a narrow absorption window, particularly in the upper GIT, i.e. stomach and duodenum. GRDDS is used for drugs that have good solubility in an acidic environment and degrade in the intestinal pH. This drug delivery system prolongs the gastric residence time of the dosage form in the stomach, leading to increased bioavailability and reducing the need for frequent dosing, promoting patient compliance. This comprehensive review article focuses on the need for the GRDDS covering all the approaches like floating, mucoadhesion, high-density, expandable etc. that conquer the gastric transit and prolong the GRT of the dosage form. It covers the role of various polymers in different approaches, along with the in vitro and in vivo evaluation techniques. This review compiles the marketed formulations of GRDDS for various diseases. It highlights the various recent advancements in the field of GRDDS, including biopolymers, 3-D printing, and nanotechnology. This paper also gives insight into the evolving application of AI and machine learning in the design, development, optimization and evaluation of GRDDS formulations.

Keywords: Gastric Retention, Bioavailability, Narrow Absorption Window, Mucoadhesive, Migrating Motor, Artificial Intelligence

How to cite this article: Sharma T, Raghavendra Rao N G, Gupta P, Sharma S, Pathak A. Conquering Gastric Transit: A Comprehensive Review of Gastroretentive Drug Delivery Systems - From Mechanistic Foundations to AI-Driven Innovations. Int J Drug Deliv Technol. 2026;16(37s): 652-670. DOI: 10.25258/ijddt.16.37s.85

Source of support: Nil.

Conflict of interest: None

1. Introduction

Oral drug delivery system is the most acceptable approach for the delivery of drugs due to advantages such as ease of administration, cost effectiveness, patient compliance, easy transportation and storage. But this system faces challenges of low bioavailability when applied to drugs having a narrow absorption window in the upper GIT because of complex GIT physiology and gastric transit, including commensal flora's pH, the surface area, and enzymatic activity[1]. This problem faced by researchers led to the development of GRDDS for better controlled release systems that increase the gastric residence time (GRT) of the dosage form in the stomach. [2,3]. The enhanced gastric retention of the dosage form increases the bioavailability and efficacy of the narrow absorption window drugs. This approach is also useful for local therapy, including treatment for gastric ulcers and infections. [4]. This review article focuses on the rationale of the GRDDS covering various factors affecting GRDDS, approaches such as floating, mucoadhesive, expandable, ion-exchange etc., including the role of polymers in different approaches. It explores critical formulation strategies with evaluation and the marketed formulations, highlighting the recent advancements in this field.

2. Rationale for GRDDS

GRDDS was developed to overcome the challenges of various biopharmaceutical limitations of conventional oral dosage forms.

- To develop an effective dosage form for the drugs with a narrow absorption window in the upper GIT.
- Improves the solubility of the drugs and helps to release them in a sustained manner.
- Useful for the drugs that are unstable in the basic environment of the intestine.
- Improves Gastric Residence Time (GRT), resulting in enhanced bioavailability.
- Provide Site-specific drug delivery with minimum systemic exposure.[5]

Table 1. Comparison of Conventional and Gastroretentive Drug Delivery Systems

Therapeutic Need	Problem with Conventional Dosage Forms	How GRDDS Addresses the Need	Example Drugs	Referen
Local Action in the Stomach	Short contact time with the disease site	Provides sustained local drug delivery	Antacids and Misoprostol	4
Narrow absorption window	Drug passes the absorption site before release.	Prolongs the release at the absorption site.	Riboflavin, levodopa	6
Low Solubility at Alkaline pH	Drug have low solubility in the intestine	Maintains the drug in a soluble state in the stomach.	Furosemide, Diazepam.	7
Short Half-Life	Requires frequent dosing	Enables once-daily dosing via prolonged release.	Lafutidine	8
Instability in the Intestine	Degradation by intestinal enzymes/pH.	Reduces exposure to the intestinal environment	Ranitidine, Metformin	9

3. Physiological Considerations for GRDDS

3.1. Gastric Anatomy and Motility

The stomach is a reservoir and acts as a grinder.The body (proximal fundus), stores undigested material. The distal antrum, or pylorus, functions as an antral pump whose peristaltic contractions mix the contents with gastric secretions and push the contents toward the pylorus. The fasted state and the fed state are the two main motility patterns that regulate the emptying of stomach contents, which does not happen continuously. [10,11]

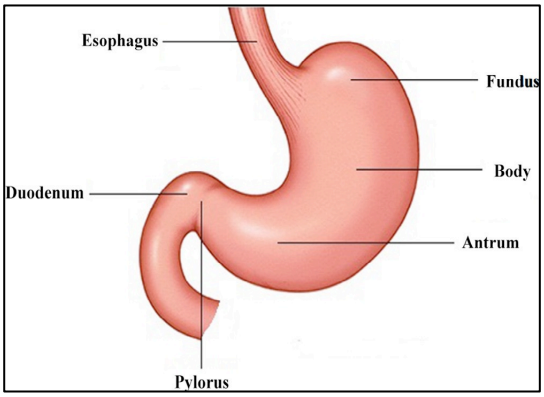

Figure 1. Anatomy of the Stomach [11]

3.2. - Fasted State-The Migrating Myoelectric Complex (MMC)

The cyclical pattern that controls the Gastrointestinal motility in the fasted state is called the Migrating Myoelectric Complex (MMC). This is a periodic cycle of electromechanical activity that recurs every 90 to 120 minutes to clear residual food, mucus, and secretions from the stomach and small intestine. Thus, the knowledge of MMC is essential for GRDDS since it is the main physiological force that a dosage form must withstand to achieve prolonged stomach retention in a fasting individual.[11,12]

3.3. The Fed State

The fed state starts as soon as a meal is consumed, interrupting the MMC. The stomach's contractions become constant and steady as it relaxes to make space for food. The calorie content and composition of the meal regulate the slower, more gradual rate at which the stomach empties.[12]

Phase	Duration (minutes)	Name of the phase	Description
Phase 1	30 to 60	Basal phase	Period of quiescence with infrequent contractions.
Phase 2	20 to 40	Pre-burst phase	Intermittent action potentials and contractions that, as the phase goes on, progressively get stronger and more frequent.
Phase 3	10 to 20	Burst phase	Brief periods of massive, frequent, strong contractions. This stage is known as the "housekeeper wave" because it enables all undigested food to pass from the stomach into the small intestine.
Phase 4	0 to 5	Transition period between Phases III and I	Occurs in a brief transitional phase between phases 1 and 3 of two successive cycles.

Table 2. Phases of the Migrating Motor Complex (MMC) [12,13]

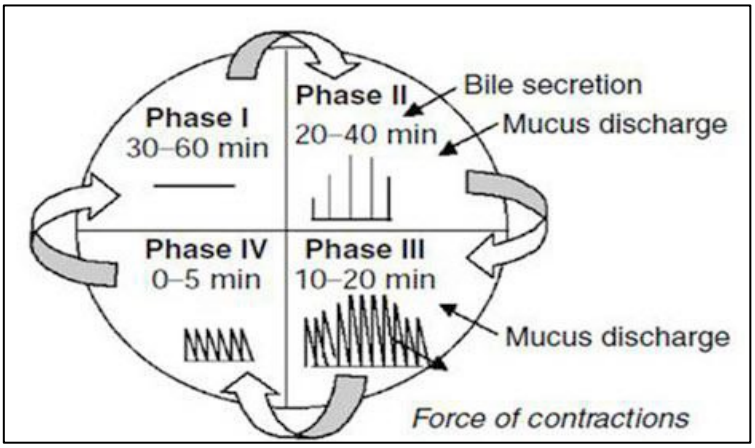

Figure 2. The four phases of MMC and their relevance to GRDDS [14]

Implication for GRDDS: A GRDDS's capacity to tolerate or prevent expulsion during Phase III of the MMC is critical to its success in the fasted state. A formulation needs to be large enough, buoyant enough, or mucoadhesive enough to withstand these strong propulsive forces. If this isn't done, the dosage form will be eliminated from the stomach.[15]

4. Factors Affecting the Performance of GRDDS

The efficacy of a gastroretentive system is influenced by various physiological, formulation-dependent factors and patient-related factors. Understanding these variables is crucial for designing an efficient GRDDS that performs consistently in a diverse patient population.

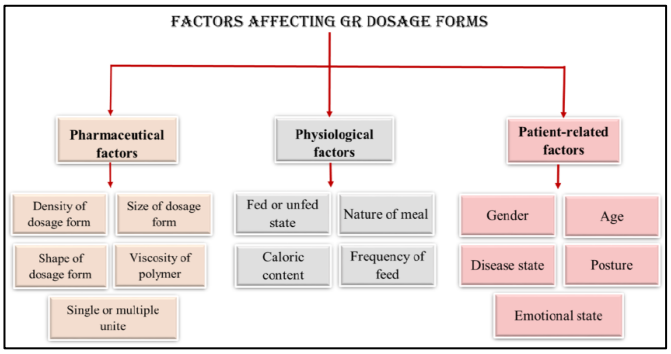

Figure 3. Factors Influencing the Performance of GRDDS [16]

4.1. Pharmaceutical Factors

4.1.1 Influence of Size and Shape of the Dosage form

The diameter and geometry of a non-floating unit dosage form determine its gastric retention time (GRT), as they influence its ability to pass through the pyloric sphincter. In the fed state, the pyloric sphincter is partially closed, allowing only particles of a certain size to pass. Dosage forms with a small size (less than 7.5 mm in diameter) pass readily with the chyme. Whereas, larger dosage forms (diameter greater than approximately 7.5 mm to 9.9 mm) are unable to pass through the constricted pylorus and are thereby retained for a longer duration. The shape of the dosage form also influences retention in the stomach. Spherical or oval tablets may pass relatively easily. However, geometries, such as ring-shaped, tetrahedral, or disk-shaped devices show more GRT.[17]

4.1.2 Role of Dosage Form Density

The maintenance of optimum density of the dosage form is the fundamental principle behind the floating GRDDS. This approach is based on maintaining a bulk density lower than that of the gastric fluids (i.e. 1.004 g/cm³) so that it floats on the gastric contents and remains in the upper part of the stomach. This protects it from the primary propulsive forces of gastric motility that are responsible for emptying content through the pylorus, thereby increasing GRT[18]. On the other hand, an increase in stomach residence time is also caused by an increase in the dosage form's density of roughly 2.5 g/cm³, which falls under high-density GRDDS.[19]

4.1.3 Influence of Polymer Viscosity

The viscosity of the gel-forming polymers is an essential parameter that influences drug release kinetics and the mechanical strength of the hydrogel layer. Polymers with lower viscosity (e.g. HPMC K100LV) show rapid hydration and gel formation, which is essential for maintaining effective buoyancy in floating and raft-forming systems. On the other hand, higher viscosity polymers (e.g. HPMC K4M) form more rigid and denser gels upon hydration, thereby increasing gel strength leading to decreased diffusion of the drug. Because of the creation of a thicker diffusion barrier, the rate of drug release usually decreases as the polymer viscosity increases [20].

4.1.4 Single-Unit versus Multiple-Unit Systems

Their gastric retention is highly variable and unpredictable in the case of Single-unit systems (e.g., monolithic tablets, floating capsules) because it depends on the transit of a single, large unit. If it passes prematurely through the pylorus, then it causes failure of the gastroretentive strategy, resulting in subtherapeutic drug levels. Also the sudden, uncontrolled drug release (dose dumping) from a single unit poses a significant safety risk, particularly for narrow therapeutic index drugs. Whereas multiple-unit systems (e.g., pellets, microspheres, granules) distribute freely within the stomach. Even if some are emptied early, this design helps them remain in place and release the medicine continuously. Because of this, there is less variability and fewer chances of an unexpected medicine release. Consequently, multiple-unit systems generally provide more reproducible drug absorption, enhanced safety, and decreased variability both within and between subjects when compared to their single-unit equivalents. [21]

4.2. Physiological Factors

A GRDDS's performance is significantly affected by the gastrointestinal tract's dynamic physiological state. The patient's food and medicine intake are the main determinants of a number of important parameters that create a dynamic environment that the dosage form must navigate. The prandial state (fed vs. fasting), meal frequency and caloric content, gastric fluid volume, and concomitant administration of medications that impact GI motility, such as prokinetic agents, anticholinergics, and opiates, are the most important of these factors. The reliable design and in vivo performance of gastroretentive systems depend on an understanding of and consideration for this physiological variability. [22,23]

4.2.1. The Prandial State: Fed versus Fasted Conditions

The Migrating Motor Complex (MMC) regulates action of the stomach during fasting state. Phase III of this cycle involves a short period of intense rhythmic contractions that clear all remaining undigested material from the stomach through the pylorus into small intestine, including the dosage form. Thus, a dosage form administered during a fasted state has more chances of being expelled and shows an unpredictable window for gastric retention. Whereas, during the fed state, MMC is disrupted, triggering gentle mixing contractions known as segmentation that break down food into chyme. During this state, only well-dispersed particles are passed through the pyloric sphincter because it is largely closed. Hence, the fed state ensures extended gastric retention, making co-administration with food a basic requirement for the success of most GRDDS.[24]

4.2.2. Impact of Caloric Content

The efficiency of gastric retention does not only depend on the presence of food in the stomach but it is also influenced by the caloric content and the nature of meal taken. The meals with high caloric value tend to prolong the gastric emptying rate and flatten the intragastric distribution. Thus, providing a suitable environment required for the GRDDS performance [25]. Lipids exhibit a more potent inhibitory effect on gastric motility compared to an isocaloric amount of carbohydrate or protein. Therefore, the higher the caloric content, the greater the delay in the gastric emptying process.[26]

4.2.3. Meal Frequency and Its Influence

The other dietary factor that affects performance of GRDDS is meal frequency. More frequent food intake maintains a continual fed (postprandial) state in the stomach, promoting the inhibition of the migrating motor complex (MMC). This favours longer and more predictable gastric residence time of the dosage form. On the other hand, extended periods of time between meals permit the natural MMC cycle to reinitiate. The onset of these strong contractions can lead to premature expulsion of the GRDDS before a sufficient quantity of drug has been absorbed,

resulting in great variability in bioavailability and possible therapeutic failure [27].

4.2.4. Volume of Gastrointestinal Fluid

The volume of the gastric fluid is another critical physiological factor, as it directly impinges on the functionality of floating and swelling-based GRDDS. Adequate volume of fluid is necessary for hydration and subsequent swelling of the polymers in swelling systems, and to start the gas-generating reaction necessary for buoyancy in effervescent floating systems. Incomplete hydration due to insufficient volume of the gastric fluid may delay the buoyancy significantly and hence severely impair the capability of the system to achieve retention [28].

4.3. Patient-Related Biological Factors

Yet, apart from these dietary and physiological conditions, a variety of intrinsic patient-related biological factors add to the great variation in GRT. It has been widely recognized that gender affects motility, as females usually exhibit slower gastric emptying than males. Another major determinant is age because gastric emptying tends to be slower in elderly patients. Several disease states may also have a profound effect on GI motility. The presence of gastric ulcers, diabetes, and hypothyroidism tends to increase GRT, and on the other hand, conditions such as hyperthyroidism and duodenal ulcers hasten gastric emptying. Even a patient's emotional state can affect their motility, with stress and anxiety delaying gastric emptying, and depression having the opposite effect [29, 30].

The posture of a patient is a critical, often-overlooked variable that differentially affects GRDDS mechanisms. In an upright, ambulatory patient, floating systems remain buoyant on the gastric contents, away from the pylorus, and thus exhibit prolonged GRT, while non-floating systems settle in the antrum and are emptied more readily. However, in a supine position, this buoyancy advantage is lost, and floating systems may be emptied faster than their non-floating counterparts [30].

5. Classification and Formulation Strategies of GRDDS

The goal of GRDDS is to decrease the gastric emptying time and extend the residence time of the dosage form in the stomach. To achieve this, various formulation strategies have been developed and these strategies have been classified based on their mechanism of action. This section deals with a comprehensive overview of these approaches.

5.1. Low-Density (Floating) Systems

There are so many strategies known for the development of GRDDS, but the floating type is the most extensively used approach. These systems are made to have a bulk density (usually less than 1.004 g/mL) that is lower than the stomach fluids so that they stay afloat above the contents of the stomach. This floating nature resists the gastric emptying and increases the dosage form's residence duration at the absorption site [31]. This system requires a high amount of fluid to float in the stomach and prevent gastric discomfort. The time required by the system to swell and float over the gastric fluids is called the floating lag time, which is a very essential parameter for the flotation of the system influenced by the properties of the polymeric matrix, including the type, viscosity grade, and concentration of the gel-forming agent. Various physiological conditions like volume of gastric fluid, fed or fasted state etc., also influence the efficacy of the floating GRDDS. As a result, using medications that irritate the stomach is not recommended for this system since prolonged contact with the stomach mucosa may exacerbate inflammation.[32,33]

The FDDS has been further divided into two types: Effervescent and Non-Effervescent Systems, depending on the mechanism of achieving buoyancy.

5.1.1. Effervescent system

This system achieves buoyancy by the formation of gas bubbles when it comes in contact with the gastric mucosa. This system is further classified on the basis of gas generation.[34]

(a) Gas-Generating Systems: This is a very common mechanism that involve the effervescent reaction between the carbonate or bicarbonate salts and the gastric acid or the co-formulated acidifiers like citric acid, tartaric acid. The carbon dioxide released during this reaction gets entrapped within the swollen polymeric matrix of polymers like HPMC, Chitosan thereby reducing its density and enabling it to float over the gastric mucosa.[35].The rate and volume of gas generation are critical; an optimal stoichiometric ratio of acid to carbonate (e.g., a citric acid to sodium bicarbonate ratio of 0.76:1 is often targeted to ensure a rapid floating lag time without causing structural disintegration.[36]

(b) Volatile Liquid–Containing Systems: These systems consist of a chamber that is filled with volatile liquid like ether or cyclopentane. When it comes in contact with body temperature, the liquid evaporates and chamber inflates which reduces the density of the system and leads to floatation. [37]

5.1.2. Non-Effervescent System

Non-effervescent floating drug delivery systems include hydrophilic polymers that undergo matrix expansion and gelation upon contact with gastric fluid, which reduces the density of the system. This increases GRT and keeps the system buoyant on the gastric contents. [38]

(a) Hydrodynamically balanced system: This system forms a colloidal gel barrier that decreases the density of the system as it involves one or more hydrophilic polymers and allowing it to float over the stomach contents.[39]

(b) Microporous compartment systems: In this technique, a microporous chamber with pores on both the top and bottom walls encloses a drug reservoir. The reservoir's external walls are hermetically sealed to prevent the undissolved drug from coming into direct contact with the stomach lining. The limited air space inside the flotation chamber allows the device to remain suspended above the contents of the stomach. As stomach fluid moves through the pores, the drug dissolves and is gradually released for absorption. [40]

(C) Hollow Microbaloons: These are also known as hollow microspheres, and their exterior polymer shells are highly laden with medication. They are created via the emulsion-solvent diffusion technique. An agitated aqueous solution of polyvinyl alcohol that was thermally controlled at 40ºC was mixed with the drug's ethanol: dichloromethane solution and an enteric acrylic polymer. Dichloromethane evaporated as a result, creating a gas phase in the dispersed polymer and an interior cavity in the polymer's microsphere that held the medication. These hollow microspheres floated continuously on the surface of an acidic dissolving liquid containing surfactant for over twelve hours.[41]

(d) Alginate beads: Alginate's high entrapment rate led to the development of a unique floating drug delivery technique that produces multi-unit floating spherical beads through the ionic gelation process. Floating alginate beads with a diameter of around 2.5 mm were made from freeze-dried calcium alginate. When an aqueous calcium chloride solution was mixed with a sodium alginate solution, the alginate precipitated. The beads were separated, snap-frozen in liquid nitrogen, then freeze-dried for 24 hours at -40ºC. As a result, a porous system that remained buoyant in the stomach and had a prolonged residence length of more than 5.5 hours was created. [42]

5.2. High-Density Systems

In contrast to floating systems, gastroretentive systems of high density are made to withstand gastric emptying by settling within the antrum of the stomach and staying in the food-filled content. The basic concept is to create a dosage form with a density significantly greater than that of gastric fluids (usually > 2.5 g/mL). This dense nature makes the system stay in the lower region of the stomach, escaping the propulsive forces of peristalsis that drain less dense content through the pyloric sphincter [43, 44]. Preparation of such systems involves high-density inert excipients in pellets, tablets, or capsules. Usually, barium sulfate, zinc oxide, titanium dioxide, and iron powder are high-density excipients used [45,46]. Despite its apparent simplicity of concept, the high-density strategy is highly challenging. It is hard to obtain uniform and sufficiently dense units in all units of a batch regularly, particularly for multi-particulate products. There are also possible safety issues associated with long-term use of heavy inert excipients. In addition, the existence of food is also a key variable; although it can facilitate retention by offering a medium for the system to settle into, the timing and content of meals can result in unforeseeable performance [44, 47].

5.3. Bioadhesive/Mucoadhesive Systems

These systems possess bioadhesive properties that enable them to adhere to the stomach mucosa after ingestion and remain in place for an extended period, despite gastrointestinal movement. Depending on the properties of the polymer, these systems can be cytoadhesive when they adhere to the epithelial surface and mucoadhesive when they adhere to the mucus layer. They produce disulfide bonds, hydrogen bonds, hydrophobic bonds, and electrostatic interactions with mucin. Inert, non-toxic, non-irritating polymers with suitable adhesion properties should be included in this formulation. The mucoadhesive qualities and contact strength are greatly influenced by the shape, flexibility, density of cross-linking, ability to form H-bonds, hydration behaviour, and charge of the polymer.[48] These systems are a great option for treating local infections. In addition to natural polymers such as sodium alginate, pectin, gelatin, and guar gum, they also contain semi-synthetic polymers, including chitosan, carbopol, lectins, polycarbophil, carboxymethylcellulose, and gliadin.[49]

Mucoadhesion Mechanism

***(a) Contact stage*:** When the mucoadhesive substance touches the mucosa, a tight wetting occurs between them. The mucus in the mucosa allows the Muco-adhesives to get wet.

***(b) Consolidation stage*:** Long-lasting mucous membrane adhesion is the outcome of the mucoadhesive material adhering to the mucous membrane through a variety of chemically and physically appealing components. This phase is known as the merging or consolidation phase. After these two stages, the mucous membrane adhesion process is finished.[50]

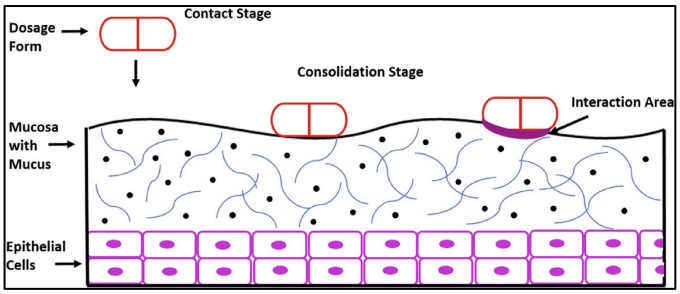

Figure 4. Mechanism of Mucoadhesion

Table 3. Theories of Mucoadhesion [51]

Theory	Bioadhesion Mechanism	Description
Electronic Theory	Favourable electrostatic interactions between the glycoprotein mucin	Electron transport between them results in the formation of a
Adsorption Theory	Chemical bonding caused by surface forces	Van der Waal's forces, hydrogen bonds, and ionic bonds are weak secondary forces;
Wetting Theory	The ability of bioadhesive polymers to spread and make	Polymers must have positive spreading coefficients.
Diffusion Theory	Mucin strands physically entangle with flexible polymer chains and penetrate the porous nature of the	For maximum diffusion and ideal bioadhesive strength, the solubility properties

Fracture Theory	Examines the highest tensile stress that occurred when the bioadhesive dosage form is separated from the mucosal surfaces.	Suitable for researching the bioadhesion of rigid polymers without flexible chains, since the actual entanglement of

5.4 Expandable, unfoldable and swellable systems

If a dosage form in the stomach is larger than the pyloric sphincter, it will survive gastric transit. The dosage form must, however, be small enough to be ingested and must not obstruct the Stomach. Therefore, to create an expandable system to extend GRT, their optimization is necessary:

1) Small oral dosage form for oral intake.
2) Enlarged gastro-retentive form.
3) Small form that allows evacuation when the medicine is released from the device.

Two methodologies are used to formulate expandable systems: either the system's unfolding qualities or its swelling features. Foldable systems are made with biodegradable polymers and APIs, folded, and placed into a pharmaceutical carrier like a gelatin capsule. For the creation of swellable systems, hydrophilic polymers such as HPMC, polyethene oxide, Carbopol, xanthan gum, pectins, gellan gum, or alginate are required. These polymers can absorb water from the stomach fluid, which can lead to polymer plasticization and swelling, an increase in the diffusion coefficient, and ultimately, polymer erosion, thereby regulating the release of the API. [52,53]

5.4 Magnetic Systems

The fundamental idea behind this technique for increasing the GRT is to attach a magnet to the abdomen above the stomach area and incorporate a tiny internal magnet into the dose form. The creation of gastroretentive magnetic nanoparticle-based formulations that will aid in the successful local and systemic administration of medications may benefit from this use. One of the main issues with using magnetic systems is that precise magnet placement can be difficult and may result in poor patient adherence.[54,55]

5.5 Raft Forming System

Raft-forming systems have garnered considerable attention for the administration of antacids and medications for gastrointestinal infections and diseases. Floating rafts have been used to treat gastric oesophageal reflux disorder (GERD). Every component of stomach fluids swells when viscous cohesive gel comes into contact with them, creating a continuous layer called a raft. One of the mechanisms involved in the formation of rafts is this process. This raft floats on stomach contents due to the low bulk density created by the CO_2 generation. Alkaline bicarbonates or carbonates that release CO_2 are typically added along with a gel-forming agent to make the system less viscous and allow it to float on the stomach contents. [56, 57]

5.6 Super Porous Hydrogels

Super porous hydrogels have an average pore size of more than 100 µm, and because of the rapid uptake of water through capillary action, they reach equilibrium size in less than a minute. The capacity of super porous hydrogels (SPH) to produce huge pores and strong swelling properties is its main mechanism. These systems use a hydrophilic polymer with cross-linking, which quickly hydrates the polymer and aids in its swelling to the proper size, further creating an open channel.[58]

5.7. Ion exchange resins

A coated ion exchange resin bead formulation laden with bicarbonates has been shown to have stomach-retentive properties. A negatively charged medication is attached to ion exchange resins that are filled with bicarbonate. To stop the quick loss of carbon dioxide, the resulting beads are subsequently enclosed in a semipermeable membrane. Chloride and bicarbonate ions are exchanged when they reach the stomach's acidic environment. In contrast to the uncoated beads, which will sink immediately, this reaction caused carbon dioxide to be generated and held in the membrane, pushing the beads toward the top of the stomach's contents and forming a layer of resin beads that floats.[59]

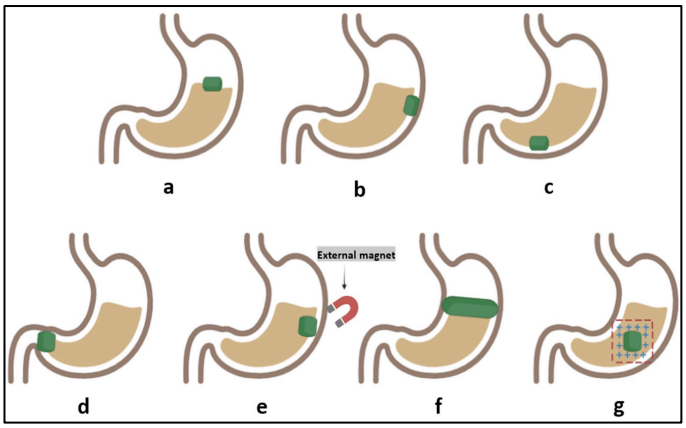

Figure 5. (a) Floating Systems, (b) Mucoadhesive Systems, (c) High-Density Systems, (d) Expandable Systems, (e) Magnetic Systems, (f) Raft-Forming Systems (g) Ion-Exchange Resin Systems.[60]

Approach	Drawbacks	Overcome Drawbacks
Floating systems	The stomach's fed condition has a significant impact on the amount of fluid required in the gastric area.	Use gas-producing effervescent chemicals to fast increase buoyancy; create low-density polymers that swiftly expand to float independent of stomach contents.
High density systems	Large medication amounts are challenging to incorporate because of technical limitations.	Optimise formulation procedures to provide increased drug loading without sacrificing density by combining with additional retention mechanisms such as bioadhesion or flotation.
Expandable systems	Biodegradable polymer storage instability; short shape memory; intricate, expensive production.	To increase shelf life, use crosslinked, more stable polymers; investigate shape-memory materials; simplify production processes; and improve packaging to increase stability.
Mucoadhesive systems	Decreased efficacy due to rapid mucus turnover and potential adherence to the incorrect mucosa (such as the oesophagus)	To improve retention, combine swelling and floating with polymers that have a balanced adhesion strength and stay in the stomach while avoiding other mucosal sites.
Magnetic systems	Patient discomfort or problems with compliance as a result of using an external magnet	Create user-friendly external magnetic devices, use smaller, biocompatible magnets integrated in dose forms, and educate patients to increase acceptability.

Table 4. Drawbacks associated with various GRDDS Approaches [61]

6. Suitable Drug Candidates for GRDDS [62,63]

GRDDS systems work best with drugs that are unstable in the intestinal environment or have a narrow absorption window that is limited to the upper gastrointestinal tract. By maintaining drug release in the stomach for extended periods of time, GRDDS increases bioavailability and reduces dose frequency, thus improving patient compliance. Selecting drugs that can benefit from prolonged stomach retention is essential to maximize the clinical effects of GRDDS.[62]

Table 5. Examples of Drugs Optimized by GRDDS

Medication	Formulation Challenge	Medical Use
Ranitidine	Requires prolonged gastric residence for local action	Management of gastroesophageal reflux disease and peptic ulcers
Levofloxacin	Instability and absorption limited to gastric environment	Management of gastric ulcers and associated infections
Amoxicillin	Targeting gastric infections with localized delivery	Part of combination regimen for eradication of Helicobacter pylori
Ciprofloxacin	Rapid plasma clearance requiring controlled release	Treatment of urinary and respiratory tract infection
Clarithromycin	Short half-life requiring sustained gastric delivery	Used in Helicobacter pylori eradication protocols
Metronidazole	Gastroretentive delivery enhances antibacterial efficacy	Effective against anaerobic infections, including H. pylori
Ofloxacin	Poor solubility at intestinal pH; gastric retention is beneficial	Used for gastrointestinal and urinary infections
Cinnarizine	Requires site-specific release to improve bioavailability	Relief of vertigo and motion sickness symptoms
Riboflavin	Narrow absorption window localized to upper GI tract	Vitamin B2 supplementation for deficiency states
Pregabalin	Narrow absorption window and rapid systemic clearance	Neuropathic pain and fibromyalgia management
Cilostazol	Absorbed mainly in proximal GI tract needing retention	Treatment of intermittent claudication
Levodopa	Stability and absorption challenges in GI tract	Parkinson's disease symptomatic treatment
Metformin	Requires controlled release to counter short half-life	Management of Type 2 diabetes mellitus
Atenolol	Poor fractional absorption beyond the stomach	Hypertension and angina pectoris treatment
Lafutidine	Absorption limited to the gastric environment	Treatment of gastric and duodenal ulcers
Verapamil	Sensitive to pH changes in GI tract	Hypertension and angina management
Captopril	Instability in alkaline environment requiring retention	Hypertension and heart failure treatment

7. Key Polymers in Different GRDDS Approaches

Polymers play a vital role in GRDDS formulations. Polymers in GRDDS are chosen based on their swelling, bioadhesive, gel-forming, or density-modifying properties, suited to the specific retention mechanism. Natural polymers, such as chitosan, xanthan gum, and sodium alginate, are appealing from a biocompatibility and biodegradability standpoint, while synthetic and/or semi-synthetic polymers, such as HPMC, Carbopol, and Ethyl Cellulose, are favourable due to their consistent mechanical strength, swelling behaviour, and control of drug release. Incorporation of polymers in GRDDS formulations are dictated by what type of gastric retention is desired, buoyancy, adhesion, swelling, or density; and the physicochemical properties of the drug to be delivered. Choice and combination of polymers may make possible the desired gastric retention time and controlled drug release for enhanced bioavailability and therapeutic effect.[63]

GRDDS Approach	Polymers Commonly Used	Functional Role
High-Density Systems	EthylCellulose, Polyvinylpyrrolidone (PVP), Hydroxypropyl Cellulose (HPC)	Increase density so dosage and remains in the stomacl
Floating Systems	Hydroxypropyl methylcellulose (HPMC), Ethyl cellulose, Carbopol, Polyvinyl alcohol (PVA), Sodium alginate, Xanthan gum	Facilitate buoyancy by sw gel formation to keep the d afloat
Swelling/Expandable Systems	HPMC, Carbopol, Xanthan Gum Polyethylene Oxide (PEO), Sodium Alginate	Rapid swelling to expand size and avoid gastric emp
Mucoadhesive/Bioadhesive Systems	Carbopol, Chitosan, HPMC,Polycarbophil, Sodium Carboxymethyl Cellulose (NaCMC), Lectins	Enhance adhesion to t mucosa, increasing retenti
Raft-Forming Systems	SodiumAlginate, Hydroxypropyl Methylcellulose (HPMC), Carrageenan, Guar Gum, Gelatin	Form a viscous gel barrier reflux and prolonging rete
Magnetic Systems	Chitosan,Polyvinyl alcohol (PVA), HPMC with magnetic particles	Carrier polymers embeddi for external magnetic cont
Superporous Hydrogel Systems	Poly(acrylic acid), HPMC, Chitosan	Capillary action allows swelling by absorbing wa linked pores.
Ion-Exchange Resin Systems	Cationic and anionic resins (water-insoluble crosslinked polymers)	Polymers release drugs exchange in stomach acid

Table 6. Functional Polymers and their applications in GRDDS [64-67]

8. Methodological Techniques for the Characterization of GRDDS [67-70]

Gastroretentive drug delivery systems (GRDDS) must be evaluated in order to guarantee its efficacy, safety, and reliable operation. Buoyancy, drug release, stomach retention duration, mucoadhesion, and mechanical strength can all be measured using a variety of in vitro, in vivo, and ex vivo techniques. Early information about the dosage form's physical features and release characteristics can be obtained by in vitro testing. In vivo studies verify how long the drug stays in the stomach and its bioavailability. Ex vivo evaluations help us understand how the dosage form interacts with biological tissues. Together, these evaluation methods support the smart development and improvement of effective GRDDS formulations.

Evaluation Parameter	Description	Purpose
Floating Lag Time	The amount of time it takes for the dosage form to float on simulated stomach fluid	To assess initial buoyancy and floating capacity
Total Floating Time	Duration the dosage form remains afloat	To measure sustained buoyancy and floating stability
Swelling Index	Degree of polymer swelling in simulated gastric medium	To evaluate swelling behaviour affecting retention
Gel Strength	Mechanical integrity of the polymer gel formed	Evaluate the robustness of the gel layer for

		retention mechanisms
Buoyancy Force Measurement	Quantitative measurement of the floating force	Quantify floating capability
Drug Content Uniformity	Consistency of drug amount in dosage units	To ensure dose accuracy and batch uniformity
In Vitro Drug Release	Drug release profile measured by dissolution testing	To determine release kinetics and sustained drug delivery
Hardness and Friability	Mechanical strength and resistance to abrasion	To assess the physical robustness of the dosage form
Drug-Excipient Interaction	Assessment by FTIR or DSC to check for incompatibility	Ensure formulation stability
Matrix Integrity Test	Visual and microscopic observation during dissolution	Check for matrix erosion or integrity over time

Table 7. In Vitro Evaluation Methods for GRDDS

Evaluation Method	Description	Purpose
Radiology (X-Ray Imaging)	Visualizing the dosage form in the stomach using radio-opaque markers	Confirm gastric retention and position
Gamma Scintigraphy	Imaging with radio-labelled formulations	Track residence time and transit
Gastroscopy	Endoscopic visualization of the dosage form	Direct observation of retention and physical state
Ultrasonography	Ultrasound imaging to monitor the dosage form	To assess the location and integrity inside the stomach
Gastrointestinal Motility	Measurement of gastric and intestinal transit times	Assess the effect on GI motility
Pharmacokinetic Studies	Measurement of plasma drug levels over time	Evaluate bioavailability and absorption
Safety and Tolerability	Monitoring adverse effects in animal/human	Ensure safety and patient compliance

Table 8. In Vivo Evaluation Methods for Gastroretentive Drug Delivery Systems

Evaluation Method	Description	Purpose
Mucoadhesion Strength	Measurement of adhesion force between the dosage form and excised gastric mucosa	To predict retention capability and effectiveness
Swelling and Erosion	Evaluation of polymer swelling and erosion in gastric fluids	Understand dosage form behaviour influencing drug
Mucosal Irritation Test	Histological examination of the mucosa after exposure	Assess biocompatibility and safety
Mechanical Properties Testing	Tensile strength, compressibility, and flexibility measurement	Evaluate robustness during handling and in the stomach

Table 9. Ex-Vivo Evaluation Methods for Gastroretentive Drug Delivery Systems

9. Marketed GRDDS Drugs (11,60,62,71)

A growing number of commercially available formulations stand as evidence of the successful translation of gastroretentive technology from a research concept to a clinically viable product. These marketed products establish therapeutic and commercial value for GRDDS in improving bioavailability, enhancing patient compliance, and achieving successful local therapy for various conditions. The following table is a comprehensive overview of some key marketed GRDDS.

Brand Name	Delivery Approach	Active Pharmaceutical Ingredient(s)	Manufacturer	Country/Region	Therapeutic Use
Madopar® HBS	Hydrodynamically balanced (floating capsule)	Levodopa, Benserazide	Roche/Intec Pharma	Europe/ Israel	Parkinson's disease
Valrelease®	Floating capsule	Diazepam	Roche	UK/USA	Anxiety

Cifran OD®	Effervescent floating tablet	Ciprofloxacin	Ranbaxy	India	Antibacterial
Oflin OD®	Floating tablet	Ofloxacin	Ranbaxy	India	Antibacterial
Glucophage® XR	Non-effervescent floating tablet	Metformin	MerckKGaA	Global	Diabetes
Liquid Gaviscon®	Raft-forming suspension	Sodium alginate, sodium bicarbonate, calcium carbonate	Reckitt	UK	GERD/Antacid
Gaviscon® Tablets	Raft-forming tablet	Sodium bicarbonate, calcium carbonate	Reckitt	UK	GERD/Antacid
Topalkan®	Raft-forming tablet	Aluminium, Magnesium hydroxide	Pierre Fabre Medicament	France	Antacid
Conviron®	Gel-forming floating tablet	Ferrous sulfate	Ranbaxy	India	Iron-deficiency anemia
Riomet OD®	Floating tablet	Metformin hydrochloride	Ranbaxy	India	Diabetes
Minextab®	Floating & swelling tablet	Metformin HCl	Galanix	France	Diabetes
Accordion Pill®	Expandable / unfolding system	Carbidopa, Levodopa	Intec Pharma	Israel, EU	Parkinson's disease
Glumetza®	Expandable tablet (AcuForm™)	Metformin hydrochloride	Depomed, Salix	USA	Diabetes
Gralise®	Expandable tablet (AcuForm™)	Gabapentin	Depomed	USA	Neuropathic pain
ProQuin XR®	Expandable tablet (AcuForm™)	Ciprofloxacin	Depomed	USA	Antibacterial
Nucynta® ER	Expandable tablet (AcuForm™)	Tapentadol	Depomed	USA	Analgesic
Janumet® XR	Expandable tablet	Sitagliptin, Metformin	Merck Sharp & Dohme	USA	Diabetes
Requip XL®	Expandable multilayer tablet (Geomatrix™)	Ropinirole	GSK	UK	Parkinson's disease
Xifaxan®	Mucoadhesive/bioadhesive tablet	Rifaximin	Lupin, Salix	USA/India	Antibiotic/GI infections
Coreg CR®	Osmotic-controlled release	Carvedilol phosphate	GSK	USA/UK	Hypertension, CHF
Cytotec®	Bilayer floating capsule	Misoprostol	Pfizer	USA/UK	Anti-ulcer
Baclofen GRS®	Multilayer swelling tablet	Baclofen	Sun Pharma	India	Muscle spasticity
LYN-005	Long-acting pill system	Risperidone	Risperidone	USA	Psychiatric disorders
Gabapentin GR®	Swelling tablet	Gabapentin	Gabapentin	USA	Pain/neuropathy

Table 10. Marketed Gastroretentive Formulations with Approaches and Therapeutic Uses

10. Advantages of Gastro-Retentive Drug Delivery System

10.1 Sustained drug delivery: The Gastroretentive drug delivery system is intended for dosage forms that release the medication in the stomach over an extended period of time.

10.2 Improved bioavailability: Compared to non-GRDDS controlled-release polymeric formulations, the bioavailability of Controlled Release-Gastro Retentive Dosage Form is significantly increased. The degree of drug absorption is influenced by a number of concurrent processes related to the movement and absorption of the medication within the gastrointestinal tract.

10.3 Improvement of absorption: Medications with low bioavailability due to site-specific absorption from the upper section of the GIT are viable options for being developed as floating drug delivery systems, thus enhancing their absorption.

10.4 Localized drug delivery system: These systems are especially beneficial for medications that are uniquely absorbed from the stomach or the upper section of the small intestine. A regulated, gradual release into the stomach ensures adequate local therapeutic concentrations with minimized systemic drug exposure. It minimizes the adverse effects that result from the medication going into the bloodstream. Moreover, the extended gastric presence due to a targeted delivery system might decrease the frequency of dosing.

10.5 Minimize variations in drug concentration: Plasma drug levels are kept within a narrower range when controlled-release gastro-retentive dosage forms are administered, as opposed to immediate-release dosage forms. As a result, concentration-related adverse effects associated with peak levels can be prevented, and variability in drug effects is decreased. This feature is especially important for drugs with a limited therapeutic index.

10.6 Reduce negative actions in the colon: The amount of medication that reaches the colon is decreased when it is retained in the stomach's HBS systems. As a result, the adverse effects of the medication in the colon could be prevented. For beta-lactam antibiotics that are only absorbed in the small intestine, where their presence in the colon encourages the development of microorganism resistance, this pharmacodynamic element supports the GRDDS formulation.[72]

11. Applications of GRDDS[73-77]

GRDDS is a novel drug delivery system that can assure sustained drug release in the stomach, hence offering immense opportunities for a wide range of therapeutic applications. Its applications range from targeted local action in the stomach itself to the improvement of systemic medication absorption with particular biological issues. The following table synthesizes the main therapeutic areas where GRDDS have shown significant clinical potential, specifying the drugs used, the main rationale for choosing a gastroretentive approach, and the resulting therapeutic benefits.

Therapeutic use	Drugs	Rationale
Cardiovascular Diseases	Atenolol, Captopril, Verapamil HCl, Nifedipine, Isosorbide mononitrate	Narrow absorption window; improved bioavailability and sustained release for chronic management.
Gastrointestinal Diseases	Misoprostol, Sucralfate, Famotidine, Ranitidine, Metronidazole	Local action in the stomach (e.g., treating ulcers, eradicating *H. pylori*); enhances efficacy and reduces systemic side effects.
Infections	Amoxicillin, Clarithromycin, Norfloxacin	Local action for *H. pylori* eradication; improved absorption for systemic antibiotics.
Neurological & Psychiatric Disorders	Levodopa/Carbidopa, Gabapentin, Venlafaxine, Risperidone	Narrow absorption window (Levodopa); sustained release for chronic condition management.
Diabetes	Metformin	Absorption window in upper GI tract; GRDDS improves bioavailability and allows for once-daily dosing.
Pain & Inflammation (NSAIDs)	Aspirin (low-dose), Ibuprofen, Diclofenac Sodium, Acetaminophen	Sustained release for prolonged analgesic effect; particularly useful for drugs with a short half-life.
Cancer	5-Fluorouracil (5-FU), Methotrexate, Busulfan, Docetaxel	Local action for gastric cancer; improves bioavailability and reduces systemic toxicity for drugs with an upper GI absorption window.

Table 11. Therapeutic Applications and Rationale of GRDDS

12. Limitations and Challenges of GRDDS

- The inter-patient variability of gastric motility depends on the age, sex and disease conditions. [78].
- The GRT of GRDDS is influenced by the nature and frequency of meals taken by the patient.[79]
- Optimum volume of fluid is required for the floating and swellable systems.[80]
- Single unit dosage form like monolithic dosage forms, may cause sudden release of the drug, causing a risk of dose dumping and adverse effects. [81].
- To develop a dosage form with minimum buoyancy lag time and maximum (approx. 12 hrs) of floatation time. [82].
- The scale-up of GRDDS is comparatively complex as compared to the conventional dosage forms, particularly in the case of multi-particulate or expandable systems.[83].
- Long-time contact with the high-concentration drug or certain excipients may lead to irritation of the mucosal lining. Such substances with gastric irritant properties must be avoided in case of GRDDS. E.g. NSAIDS. [84]
- Systems that are large, swellable or expandable may possess a risk of GIT obstruction if not designed properly.[85]
- Long-term toxicity evaluation of novel, magnetic or high-density polymers is essential to ensure safety during chronic disease administration. [86]
- The verification of gastric retention involves complex techniques like gamma scintigraphy or MRI, which increases the developmental cost and time.[87]
- Lack of biorelevant in vitro models that could predict in vivo performance. The conventional dissolution apparatuses do not possess the dynamic mechanical forces working in the human stomach.[88]
- Developing bioequivalence between generic GRDDS and its corresponding product is challenging due to the various variability factors.[89]

13. Recent Advancements and Future Perspectives in GRDDS

Recent innovations are focused on creating more intelligent, reliable, and patient-specific systems that provide safe retention and precision therapy. This section covers the technologies at the cutting edge that push the boundaries in gastroretentive drug delivery. [90]

13.1 Hybrid and Combinational Systems:

Recognising such a limitation, there has been an increasing amount of research in the development of hybrid methods involving two or more retention strategies. This provides a synergistic effect "fail-safe" phenomenon, ensuring gastric retention even if one mechanism is compromised by physiological variability. [91]

(a) Floating-Mucoadhesive Systems: Such dual-action systems are designed to float on gastric contents while forming a strong bioadhesive bond with the stomach wall. This approach, in particular, could be effective in overcoming the "all-or-nothing" gastric emptying during Phase III of the Migrating Motor Complex (MMC). For example, studies on glyceryl monooleate-coated hollow-bioadhesive microspheres have shown excellent floating behaviour combined with enhanced mucoadhesion, both resulting in longer, more predictable gastric retention times. [92]

(b) Floating-Expandable Systems: This strategy combines immediate buoyancy with the long-term mechanical barrier of swelling. The dosage form is small for easy ingestion, rapidly floats to avoid early emptying, and then swells to a size that physically prevents its passage through the pyloric sphincter. The proper application of super-disintegrants along with highly swellable polymers, such as polyvinyl alcohol and polyethene oxide, is very important in achieving rapid and significant swelling for this mechanism. [93]

13.2. Nanotechnology-Enabled Precision Delivery

Nanotechnology integration opened new ways for targeted and efficient therapy, mainly for local action in the stomach and for drugs with stability issues. [94]

(a) Mucoadhesive Nanocarriers: Chitosan-coated and lectin-conjugated nanoparticles exhibit superior mucoadhesion and, therefore, can attach themselves firmly to the gastric mucosa, providing sustained local drug release. This is particularly advantageous for antibiotics in Helicobacter pylori eradication because of the increased contact time of the drug with the embedded bacteria. [95]

(b) Floating Nanocarriers: Nanosystems prepared from low-density materials, like Eudragit RS, or hollow-structured nanoformulations (e.g., microballoons) can float on an empty stomach. This can ensure a high local concentration of the drug at the site of absorption and thus may be able to overcome problems related to short gastric residence times of conventional dosage forms. [96]

13.3. 3D Printing:

The additive manufacturing technique is revolutionising the fabrication of GRDDS by allowing for complex geometries and personalised dosages that are impossible to achieve with traditional compression. [97]

(a) Precision Engineering of Buoyancy and Release: Techniques such as Fused Deposition Modelling and Semi-Solid Extrusion provide the possibility to fabricate dosage forms with complex internal channels and with infill patterns of low density. Thus, this enables immediate floating and allows for sophisticated, tailored drug release profiles, including dual-pulsatile or zero-order release from a single unit. [98]

(b) Personalized Medicine: 3-D printing helps to fabricate a patient-specific dosage form with the required dose, release profile and dimensions. This technique overcomes the challenges associated with inter-patient variability and leads to the development of personalized medicine.[99]

13.4 Stimuli-Responsive "Smart" Polymeric Systems

Advanced polymers have been discovered, known as Smart Polymers, that are capable of responding to specific physiological stimuli [100]. These type of polymers have been discussed below.

(a) pH-Responsive Polymers: These polymers remain stable in a specific pH that allows continuous release of drug and degrade in different pH. These pH-responsive polymers are applicable in GRDDS as they remain stable in acidic conditions of the stomach and dissolve in basic or intestinal Ph, resulting in safe evacuation and minimized unintended long gastric retention like Eudragit® E PO.[101]

(b) Enzyme-Responsive Systems: These polymers degrade in the presence of enzymes that are associated with specific enzymes, such as urease produced by Helicobacter pylori. This approach enables target-specific release of drug, leading to enhanced therapeutic efficacy, minimized systemic exposure and side effects. [102]

13.5. Advanced and Sustainable Biopolymers

The increased interest in the field of eco-friendly and biocompatible excipients has led to extensive research resulting in the innovation and development of biodegradable polymers with some alterations that enhanced their functionality.[103]

(a) Chemically Modified Biopolymers: Natural Polymers with chemical modifications have better functional properties. E.g. Thiolated chitosan has improved mucoadhesive strength and controlled release profile than unmodified chitosan. [104]

(b) Synergistic Polymers Combinations: Dosage forms with more than one biopolymeric blend show better results due to synergistic interactions. E.g. Gellan gum-Xanthan gum and Chitosan-Pectin combinations show enhanced properties like gel strength, mucoadhesion and controlled release profile.[105]

13.6. Applications of Artificial Intelligence and Machine Learning in GRDDS

GRDDS development requires optimization of multiple variables, that is conventionally done by applying Design of Experiments (DOE). The nonlinear interactions among

formulation and process variables, as well as in vivo performance, are complicated to decipher. However, with the inclusion of AI and ML, things are changing. Both AI and ML enable the shift from experimentation to data-driven predictive science. These smart systems are useful for progress.[106] AI has already been applied across the pipeline with success, such as in the GRDDS development. They seem helpful for formulation optimisation, as they make accurate performance predictions.

(a) Advanced Formulation Optimization via Supervised and Unsupervised Learning

The application of AI in GRDDS is well in progress. It involves using supervised ML for QFPR modelling. Much research exists on the topic. Algorithms like ANNs and SVR usually perform better. They beat traditional statistical models. This is true when predicting key quality attributes. [107, 108]

- **Optimizing Floating Tablets:** Shan et al., in a direct comparative study, revealed that an ANN substantially outperformed RSM in optimizing a floating GRDDS for metformin HCl. The ANN model developed using the concentrations of HPMC K4M, Carbopol 974P, and sodium bicarbonate as inputs resulted in a better correlation ($R^2 > 0.99$) in predicting the floating lag time and drug release profiles, thus successfully identifying an optimal formulation which was experimentally validated.[109]
- **Mucoadhesive Systems Design**: Besides floating systems, the application of ML is extended. Patil et al. 2020 utilized ANN to model a mucoadhesive GRDDS, in which the model has shown reasonable prediction of bioadhesive strength and drug release for chitosan and Carbopol 934P concentration.[110]

b. Improved Pharmacokinetic Prediction and Advanced IVIVC Modelling

One of the most important research frontiers is the use of AI to establish a link between in vitro performance and in vivo results. The main reason for this is the failure of traditional IVIVC for complex GRDDS, which has led to the invention of AI-powered modelling techniques.

- **Machine Learning-enhanced IVIVC:** Mendez et al. (2023) reported the development of a novel approach by applying ML algorithms to correlate complex in vitro dissolution profiles, including biorelevant media data, to in vivo pharmacokinetic parameters for modified-release formulations. This technique showed superior predictive accuracy compared to linear correlation methods and hence provided a powerful new tool for the de-risking of GRDDS development. [112]
- **AI in PBPK Modelling:** Linking ML with Physiologically-Based Pharmacokinetic models is a significant landmark. In this regard, ML is used to simplify and individualize parameters of the PBPK model. Schneck et al., 2022, demonstrated that ML-based methods could modify system-specific parameters, such as gastric emptying time distributions, to provide a more accurate prediction of the "virtual population" for drug product performance under varying physiological conditions.[113]

(c) AI in Advanced Manufacturing and Real-Time Process Control

The transition to sophisticated GRDDS, like 3D-printed devices, has resulted in a harmonious relationship with AI for process optimization. They are actively being researched and implemented to guarantee the regular production of complex dosage forms.

- **Optimizing 3D Printing of GRDDS:** The fabrication of GRDDS by means of 3D printing enables geometrically complicated shapes that support buoyancy. Wang et al. (2023) harnessed machine learning to optimize the semi-solid extrusion 3D printing of a gastric-floating tablet. The ML model they used learned how to relate the complex interactions between printing parameters, such as pressure and speed, with the hardness and buoyancy properties of the printed tablets. It enabled the fast creation of dosage forms with pre-defined gastro-retentive characteristics. [114] This is an example of using AI to fabricate a functional GRDDS.
- **Process Analytical Technology (PAT) and ML: PAT and ML:** In multi-particulate GRDDS, consistent pellet size and density are crucial to ensure predictable gastric retention. Koller et al., 2011, showed that data from NIR spectroscopy, one of the PAT tools, can be combined with multivariate data analysis (a forerunner of modern-day ML) to monitor and predict, in real-time, the properties of the granules throughout a fluidized bed process. [115] The ML algorithms of today pick up from here, utilizing such PAT data for real-time quality control in the manufacturing process of multi-unit GRDDS.

(d) Data-Driven Insights and Preclinical Planning

AI is also being applied to extract deeper insights from existing data and to optimize the preclinical testing phase.

- **Predicting Drug-Excipient Compatibility:** A very important and necessary first step in the whole formulation process is drug and polymeric matrix compatibility. Artificial Intelligence (AI) modelling done using gigantic chemical databases works daily to predict the possible interactions between drugs and excipients. According to Bannigan et al. (2023), these models could be used to screen virtual polymer libraries and then select stable and compatible candidates for the drug, thus lowering the risks associated with the first steps of GRDDS development. [106]

Application Area	Specific AI/ML Technique	Purpose	Outcome	References
Formulation Optimization	Artificial Neural Networks (ANNs)	QFPR modelling to predict floating lag time, total floating time, and drug release profile.	ANN models outperformed traditional RSM, achieving $R^2 > 0.99$ in predicting metformin release from a floating GRDDS and accurately identifying the optimal formulation.	109
Formulation Optimization	Support Vector Regression (SVR), Random Forest	Predict complex drug release kinetics and identify critical excipient attributes.	ML models can handle non-linear relationships, providing more accurate predictions than linear models. Random Forest can rank excipient importance (e.g., HPMC viscosity grade).	108
In-Vitro-In Vivo Correlation (IVIVC)	Various ML Algorithms (e.g., ANN, SVR)	Develop non-linear IVIVC models by correlating complex in vitro dissolution data with in vivo PK parameters.	ML-driven IVIVC provided higher predictive accuracy for modified-release formulations compared to conventional linear methods, crucial for GRDDS.	112
Pharmacokinetic Prediction	ML-enhanced PBPK Modeling	Refine PBPK model parameters to simulate GRDDS performance in virtual populations, accounting for food effects and variability.	Integration of ML allows for better individualization of parameters like gastric emptying time, creating more accurate "digital twins" for in silico testing.	113
Advanced Manufacturing	Machine Learning	Optimize critical parameters in 3D printing (e.g., pressure, speed) to fabricate GRDDS with specific buoyancy and release properties.	ML models successfully learned the relationship between printing parameters and tablet CQAs, enabling rapid production of optimized floating tablets.	114
Quality Control	Computer Vision / Convolutional Neural Networks (CNNs)	Automated, real-time visual inspection of multi-particula	ML-based vision systems can identify critical defects (micro-	116

		te or 3D-printed GRDDS to detect defects.	fissures, shape deformities) that could compromise gastroretention, ensuring batch quality.	
Pre-Formulation Studies	Natural Language Processing (NLP) & Predictive ML	AI scientific literature and chemical data to predict drug-excipient compatibility and identify promising polymer candidates.	AI can accelerate the pre-formulation stage by screening virtual excipient libraries and predicting stability, de-risking initial development.	106
Personalized Therapy	Machine Learning	Analyze patient-specific data (e.g., gastric emptying rate from diagnostic tests) to predict optimal drug release profile.	While still emerging, the concept involves using AI to tailor GRDDS design or select a pre-programmed release profile for a specific patient's physiology.	120

Table 12. AI-Driven Strategies for GRDDS

14. Future Perspectives

The future of GRDDS is expected to evolve into intelligent and personalized medicine. The main prospects are as follows:

14.1. Digital Integration: The real-time monitoring of the gastric retention and physiologic data could be done by integrating small ingestible sensors within smart pills, providing information to clinicians about medication adherence and performance.[117]

14.2. AI-Driven Formulation: GRDDS development requires analysis of complex data that can be easily done by using AI and Machine Learning models, which saves time and cost required to develop an optimized and effective dosage form.[106]

14.3. Delivery of Biologics: The delivery of biologics like peptides, proteins and nucleic acids involves designing the protective gastric depot having permeation enhancers and enzyme inhibitors.[118]

14.4. Advanced Manufacturing: 4D printing will be used to fabricate devices that change shape inside the stomach in response to gastric stimuli, ensuring mechanical retention followed by safe disintegration. [119]

15. Identified Research Gaps and Future Directions

Despite the substantial progress, many critical research gaps persist and offer an opportunity for further investigation:

15.1. IVIVC Gap: The most important challenge today, however, is the absence of in vitro dissolution and retention studies that are capable of predicting the dynamic, biologically active conditions found within the human stomach concerning its contraction and motility pattern, shear forces, and fluctuating pH and volume. The development of more biorelevant and mechanically dynamic in vitro apparatuses is considered highly crucial to enhance the predictive power of pre-clinical studies and reduce the high failure rates in clinical development.

15.2. Safety of Long-term Gastric Retention: There is a paucity of long-term toxicological data on the continuous exposure of the gastric mucosa to high concentrations of drugs and polymeric excipients from GRDDS. Systematic studies are needed to evaluate the potential for chronic irritation, mucosal damage, or unforeseen complications, particularly for drugs meant for lifelong management of chronic diseases.

15.3. Standardization and Robustness for Clinical Translation: The performance of many gastroretentive drug delivery systems is variable and influenced by factors such as prandial state and individual physiological differences. The formation of harmonized regulatory frameworks and strong bioequivalence protocols for generic GRDDSs continues to be one of the important challenges.

16. Conclusion

GRDDS is a promising approach to counter the challenges faced by conventional oral drug delivery systems. This delivery system is useful for drugs that have a narrow absorption window and pH-dependent solubility to enhance the bioavailability of the drug. GRDDS overcomes the challenge of early gastric transit of the dosage form by prolonging the gastric residence time of the dosage form by using various formulation

approaches like floating, high density, mucoadhesion, swellable and expandable systems based on the type of polymer used and the unique mechanism each system follows to enhance the gastric residence and bioavailability of the drug. The successful design and development of GRDDS has led to the various marketed formulations used for various diseases. Continuous research is going on to inculcate new and advanced techniques to this field like nanotechnology, use of smart polymers and biopolymers, 3-D printing and various AI and machine learning models to design, develop, optimize and evaluate the novel GRDDS.

REFERENCES

1. Lopes CM, Bettencourt C, Rossi A, Buttini F, Barata P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. Int J Pharm. 2016;510:144-58.
2. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: an overview. Drug Dev Ind Pharm. 1996;22:531-9.
3. Groning R, Heun G. Oral dosage forms with controlled gastrointestinal transit. Drug Dev Ind Pharm. 1984;10(4):527-39.
4. Shinde S, Tadwee I, Shahi S. Gastrortentive Drug Delivery System. Int J Pharm Res Allied Sci. 2011;1(2):7-8.
5. Martin S, Sundaram IS. Gastro Retentive Drug Delivery Systems (GRDDS) - Comprehensive Review. J Neonatal Surg. 2025;14.
6. Levy G, Jusko WJ. Factors affecting the absorption of riboflavin in man. J Pharm Sci. 1966;55:285-9.
7. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. J Pharm Sci. 1994;83:239-45.
8. Patel A, Jain D. Design and Optimization of Low-Density Gastroretentive Polymeric Microballoons for the Supply of Lafutidine in the Management of Peptic Ulcer. Pharma Sci Anal Res J. 2024;6(2):180049.
9. Chandira RM, Palanisamy P, Jaykar B. Formulation and evaluation of bilayered floating tablets of metformin hydrochloride. Int Res J Pharm. 2012;3:257-67.
10. Patil H, Tiwari RV, Repka MA. Recent advancements in mucoadhesive floating drug delivery systems: A mini-review. J Drug Deliv Sci Technol. 2016;31:65-71.
11. Mandal UK, Chatterjee B, Senjoti FG. Gastro-retentive drug delivery systems and their in vivo success: A recent update. Asian J Pharm Sci. 2016;11:575-84.
12. Prajapati VD, Jani GK, Khutliwala TA, Zala BS. Raft Forming System—An Upcoming Approach of gastroretentive drug delivery system. J Control Release. 2013;168:151-65.
13. Badhan AC, Mashru RC, Shah PP, Thakkar AR, Dobaria NB. Development and evaluation of sustained release gastroretentive minimatrices for efficient delivery of metronidazole and amoxicillin to treat gastric ulcers. Indian J Pharm Sci. 2009;71(1):55-62.
14. Landge P, Lavande J, Swami A, Dharashive V. A Review on Gastroretentive Drug Delivery System. Res J Pharm Dos Forms Technol. 2023;15(1):62-8. doi: 10.52711/0975-4377.2023.00011.
15. Singh RP, Rathore DS. Gastroretention: a means to address local targeting in the gastric region. Pharmacophore. 2012;3(6):287-300.
16. Khalaf MM, Alinejad SS, Sajad O, Abdul Rasool BK. Gastro-retentive drug delivery technologies and their applications with cardiovascular medications. J Popul Ther Clin Pharmacol. 2023;30(5).
17. Hatwar RP, Channawar MA. Gastroretentive Mucoadhesive Drug Delivery System. World J Pharm Res. 2020;8:819-20.
18. Chauhan MS, Kumar A, Pathak K. Osmotically regulated floating asymmetric membrane capsule for controlled site-specific delivery of ranitidine hydrochloride: optimization by central composite design. AAPS PharmSciTech. 2012;13:1492-501.
19. Clarke GM, Newton JM, Short MB. Gastrointestinal transit of pellets of differing size and density. Int J Pharm. 1993;100:81-92.
20. Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and Carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int J Pharm. 2003;253(1-2):13-22.
21. Efentakis M, Koutlis A, Vlachou M. Development and evaluation of oral multiple-unit and single-unit hydrophilic controlled-release systems. AAPS PharmSciTech. 2000;1(4):E33.
22. Pahwa R, Piplani M, Sharma PC, Kaushik D, Nanda S. Orally administered gastroretentive drug delivery systems: a review. Curr Drug Deliv. 2012;9(6):577-85.
23. Vinchurkar K, Sainy J, Khan MA, Mane S, Mishra DK, Dixit P. Features and facts of a gastroretentive drug delivery system: a review. 2022;13:903450.
24. Deloose E, Janssen P, Depoortere I, Tack J. The migrating motor complex: control mechanisms and its role in health and disease. Nat Rev Gastroenterol Hepatol. 2012;9(5):271-85.
25. Marciani L, Cox E, Garsed KC, Pritchard S, Totman JJ, Hoad CL, et al. Measurement of gastric emptying rate and intragastric meal distribution by magnetic resonance imaging. Magn Reson Med. 2014;71(3):1080-6.
26. Chong PP, McCullough KA, Staines A, Dhar P, Kochhar G, Kumar D. Effect of caloric and nutrient content of oral fluids on gastric motility and emptying: A systematic review. Neurogastroenterol Motil. 2024;36(2):e14400.

27. Shidhaye S, Kate N, Kadam V. Effect of food on bioavailability of drug through gastro-retentive drug delivery system. Bioequiv Bioavailab Int J. 2021;5(1):000148.
28. Shinde S, Pawar S, Kadam V. Gastro retentive drug delivery system: a review. World J Pharm Sci. 2016;5(7):236-45.
29. Prinderre P, Sauzet C, Fuxen C. A comprehensive update on gastroretentive drug delivery systems: fundamentals and applications. Pharmaceutics. 2020;12(2):123.
30. Talukder R, Fassihi R. Gastroretentive delivery systems: a mini review. Drug Dev Ind Pharm. 2004;30(10):1019-28.
31. Namdev A, Jain D. Floating drug delivery systems: An emerging trend for the treatment of peptic ulcer. Curr Drug Deliv. 2019;16(10):874-86.
32. Mudie DM, Amidon GL, Amidon GE. Physiological parameters for oral delivery and in vitro testing. Mol Pharm. 2010;7:1388-405.
33. Jassal M, Nautiyal U, Kundlas J, Singh D. A review: gastroretentive drug delivery system (GRDDS). Indian J Pharm Biol Res. 2015;3:82-92.
34. Garg S, Sharma S. Gastroretentive drug delivery systems. Bus Briefing: Pharmatech. 2003;160-6.
35. Strübing S, Abboud T, Contri RV, Metz H, Mäder K. New insights into the impact of sodium bicarbonate on the swelling and release mechanisms of effervescent floating tablets. Eur J Pharm Sci. 2018;123:201-11.
36. Zhao Q, Li L, Zhu T. Optimization of a floating tablet containing citric acid and sodium bicarbonate and its evaluation in vitro and in beagle dogs. Drug Dev Ind Pharm. 2020;46(4):559-68.
37. Krogel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. Int J Pharm. 1999;187(2):175-84.
38. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 2000;63(3):235-59.
39. Goole J, Vanderbist F, Amighi K. Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. Int J Pharm. 2007;334:35-41.
40. Goyal M, Prajapati R, Purohit KK, et al. Floating Drug Delivery System. J Curr Pharm Res. 2011;5(1):7-18.
41. Khanam N, Alam I, Mian SS, Srinivas N. A review on novel approaches incorporated in the formulation of gastro retentive drug delivery system. Pharm Sci Int J Pharm Biol Sci. 2017;7:52-60.
42. Sen O, Manna S, Nandi G, Jana S. Recent advances in alginate based gastroretentive technologies for drug delivery applications. Med Nov Technol Devices. 2023;18:144-58.
43. Bechgaard H, Ladefoged K. Distribution of pellets in the gastrointestinal tract. Influence on transit time exerted by the density or diameter of pellets. J Pharm Pharmacol. 1978;30(1):690-2.
44. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop J Pharm Res. 2008;7(3):1055-66.
45. Whitehead L, Fell JT, Collett JH. Development of a gastroretentive dosage form. Eur J Pharm Sci. 1998;6(1):71-7.
46. Kavanagh N, Corrigan OI. Swelling and erosion properties of hydroxypropylmethylcellulose (Hypromellose) matrices—influence of agitation rate and dissolution medium composition. Int J Pharm. 2004;279(1-2):141-55.
47. Narendra C, Srinath MS, Babu G. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. AAPS PharmSciTech. 2006;7(2):E23-9.
48. Andrews GP, Laverty TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. Eur J Pharm Biopharm. 2009;71(3):505-18.
49. Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Deliv Rev. 2005;57(11):1556-68.
50. Boddupalli BM, Mohammed ZN, Nath RA, Banji D. Mucoadhesive drug delivery system: An overview. J Adv Pharm Technol Res. 2010;1(4):381-7.
51. Carvalho FC, Bruschi ML, Evangelista RC, Gremião MPD. Mucoadhesive drug delivery systems. Braz J Pharm Sci. 2010;46(1):1-17.
52. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J Control Release. 2003;90(2):143-62.
53. Abubakar O, Nur Jun S, Zhang. Recent progress in sustained: controlled oral delivery of captopril: an overview. Int J Pharm. 2000;139-146.
54. Awasthi R, Kulkarni GT. Decades of research in drug targeting to the upper gastrointestinal tract using gastroretention technologies: Where do we stand? Drug Deliv. 2016;23:378-94.
55. Sravya K, Kavitha K, Rupesh Kumar M, Jagdeesh Singh SD. Gastroretentive drug delivery systems: A review. Res J Pharm Biol Chem Sci. 2012;3(3):966-80.
56. Chaturvedi S, Kumari P, Singh S, Agrawal V. Approaches to increase the gastric residence time; floating drug delivery systems - A review. Asian J Pharm Clin Res. 2013;6(3):1-9.
57. Shah S, Patel J, Patel N. Stomach specific floating drug delivery system: A review. Int J PharmTech Res. 2009;1(3):623-33.
58. Omidian H, Rocca JG, Park K. Advances in superporous hydrogels. J Control Release. 2005;102(1):3-12.

59. Gupta R, Tripathi P, Bhardwaj P, Mahor A. Recent advances in gastro retentive drug delivery systems and their application on the treatment of H. pylori infections. J Anal Pharm Res. 2018;7(4).
60. Turac IR, Porfire A, Iurian S, Crisan AG, Casian T, Iovanov R, Tomuta I. Expanding the manufacturing approaches for gastroretentive drug delivery systems with 3D printing technology. Pharmaceutics. 2023;15(8):1983.
61. Pawar VK, Kansal S, Asthana S, Chourasia MK. Industrial perspective of gastroretentive drug delivery systems: Physicochemical, biopharmaceutical, technological and regulatory consideration. Expert Opin Drug Deliv. 2012;9:551-65.
62. Tripathi J, Thapa P, Maharjan R, Jeong SH. Current state and future perspectives on gastroretentive drug delivery systems. Pharmaceutics. 2019;11.
63. Menon A, Menon S. A review on gastroretentive drug delivery systems. PharmaTutor. 2016;4(2):47-56.
64. Dhamale GR, Shelke HL, Shinde PB, Khedkar RR, Rohokale PP, Rajguru JR. Gastroretentive drug delivery systems: A review. Int J Pharm Sci. 2024.
65. Ainurofiq A, Daryati A, Murtadla FA, Salimah F, Akbar NM, Faizun R. The use of natural and synthetic polymers in the formulation of gastroretentive drug delivery systems. Int J Drug Deliv Technol. 2023;13(1):435-44.
66. Waqar MA, Mubarak N, Khan AM, Khan R, Shaheen F, Shabbir A. Advanced polymers and recent advancements on gastroretentive drug delivery system: A comprehensive review. J Drug Target. 2024;32(6):655-71.
67. Chouhan P, Tripathi P, Nayak S. Exploring the role of polymers in sustained gastroretentive drug delivery systems. Int J Nurs Med Sci. 2025;14(4):1-9.
68. Senjoti FG, Lee SW, Kim JS, Gupta VK, Sohal JS, Cho JK. Design and in-vitro evaluation of sustained release gastroretentive drug delivery systems. J Pharm Pharmacol. 2016;68(3):355-67.
69. Ahmed M, Alomari MM, Shalah J, Goma MA, Patel RP, Basit AW. Current state and future perspectives on gastroretentive drug delivery systems. Drug Dev Ind Pharm. 2019;45(4):573-83.
70. Schneider F, Koziolek M, Weitschies W. In vitro and in vivo test methods for the evaluation of gastroretentive dosage forms: understanding human gastrointestinal physiology implications. Expert Opin Drug Deliv. 2019;16(8):745-56.
71. Vrettos NN, Andreadis T, Katsavou A, Tsagkaris C, Zachariadou M, Valsami G, et al. Gastroretentive technologies in tandem with controlled release strategies: A potent synergistic approach for advanced oral drug delivery. Pharmaceutics. 2021;13(10):1647.
72. Vantimitta SR, Jeganath S. Novel approaches of gastro retentive drug delivery system: A review. Int J Health Sci. 2022;6(S1):3464-76.
73. Lonkar AM, Ajabe RG, Akhand VG, Katekar VA, Deshmukh NB, Deshmukh SP. Formulation and evaluation of gastroretentive drug delivery system. Int J Pharm Sci Dev Res. 2024;10(1):1-7.
74. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. Expert Opin Drug Deliv. 2006;3(2):217-33.
75. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: a review. AAPS PharmSciTech. 2005;6(3):E372-90.
76. Badhan AC, Mashru RC, Shah PP, Thakkar AR, Dobaria NB. Development and evaluation of sustained release gastroretentive minimatrices for efficient delivery of metronidazole and amoxicillin to treat gastric ulcers. Indian J Pharm Sci. 2009;71(1):55-62.
77. Hua S. Advances in oral drug delivery for regional targeting in the gastrointestinal tract - Influence of physiological, pathophysiological and pharmaceutical factors. Front Pharmacol. 2020;11:524.
78. Hellström PM, Grybäck P, Jacobsson H. The physiology of gastric emptying. Best Pract Res Clin Anaesthesiol. 2011;25(1):1-11.
79. Koziolek M, Alcaro S, Augustijns P, Basit AW, Grimm M, Hens B, et al. The stomach and its role in controlling drug delivery and bioavailability. Int J Pharm. 2020;579:119121.
80. Goyal S, Thakkar R, Mishra N. Impact of acid-reducing agents on the performance of gastroretentive drug delivery systems: A mechanistic review. J Pharm Sci. 2021;110(3):1025-35.
81. Huang Y, Wang C. Recent advances in gastroretentive drug delivery systems for controlled release of drugs with narrow therapeutic index. Drug Deliv Transl Res. 2020;10(5):1307-22.
82. Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization and in vitro-in vivo evaluation in healthy volunteers. Int J Pharm. 2015;485(1-2):210-22.
83. Norman J, Madurawe RD, Moore CM, Khan MA, Khairuzzaman A. A new chapter in pharmaceutical manufacturing: 3D-printed drug products. Adv Drug Deliv Rev. 2017;108:39-50.
84. Kagan L, Hoffman A. Selection of drug candidates for gastroretentive dosage forms: pharmacokinetics following continuous intragastric mode of administration in a rat model. Eur J Pharm Biopharm. 2008;69(1):238-46.
85. Lennernäs H, Knutson L, Knutson T, Hussain A, Lesko L, Salmonson T, et al. The effect of amoxicillin on human

gastric acid secretion and pharmacokinetics of amoxicillin. J Control Release. 2013;172(1):210-7.
86. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: overview and special case of Helicobacter pylori. J Control Release. 2006;111(1-2):1-18.
87. Weitschies W, Wilson CG. In vivo imaging of drug delivery systems in the gastrointestinal tract. Int J Pharm. 2011;417(1-2):216-26.
88. Garbacz G, Klein S. Dissolution testing of oral drug delivery systems: current and future perspectives. Pharm Res. 2022;39(5):791-801.
89. Davit BM, Conner DP. The US Food and Drug Administration's perspective on the development of generic locally acting gastrointestinal drugs. Clin Pharmacol Ther. 2019;106(1):83-95.
90. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. Expert Opin Drug Deliv. 2006;3(2):217-33.
91. Vrettos NN, Roberts CJ, Zhu Z. Gastroretentive technologies in tandem with controlled-release strategies: a potent answer to oral drug bioavailability and patient compliance implications. Pharmaceutics. 2021;13(12):2161.
92. Liu Y, Zhang J, Gao Y, Zhu J. Preparation and evaluation of glyceryl monooleate-coated hollow-bioadhesive microspheres for gastroretentive drug delivery. Int J Pharm. 2011;417(1-2):103-9.
93. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J Control Release. 2003;90(2):143-62.
94. Date AA, Hanes J, Ensign LM. Nanoparticles for oral delivery: design, evaluation and state-of-the-art. J Control Release. 2016;240:504-26.
95. Umanaheshwari RB, Jain NK. Receptor-mediated targeting of lectin-conjugated gliadin nanoparticles in the gastrointestinal tract. J Drug Target. 2003;11(5):259-67.
96. Jain SK, Awasthi AM, Jain NK, Agrawal GP. Calcium silicate-based microspheres of repaglinide for gastroretentive floating drug delivery: preparation and in vitro characterization. J Control Release. 2005;107(2):300-9.
97. Vithani K, Goyanes A, Jannin V, Basit AW, Gaisford S, Boyd BJ. An overview of 3D printing technologies for the fabrication of gastroretentive drug delivery systems. Int J Pharm. 2020;589:119839.
98. Mora-Castaño G, Millán-Jiménez M, Linares V, Caraballo I. Hydrophilic high drug-loaded 3D printed gastroretentive floating tablets. Pharmaceutics. 2023;15(3):757.
99. Goyanes A, Madla CM, Umerji A, Piñeiro GC, Montero JM, Diaz MJ, et al. Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: first single-centre experience. Int J Pharm. 2019;570:118658.
100. Gupta P, Vermani K, Garg S. Hydrogels: from controlled release to pH-responsive delivery. Drug Discov Today. 2002;7(10):569-79.
101. Thakral S, Thakral NK, Majumdar DK. Eudragit® E PO based pH-responsive loating hydrogels for gastroretentive drug delivery: design, synthesis, and in vitro characterization. Drug Dev Ind Pharm. 2020;46(7):1053-63.
102. Zhang Y, Wu XY. Enzymatically degradable gastroretentive drug delivery systems for site-specific antibiotic release in the stomach. J Control Release. 2021;329:1212-23.
103. Ainurofiq A, Choiri S. The use of natural and synthetic polymers in the formulation of gastroretentive drug delivery systems. Int J Drug Deliv Technol. 2023;13(1):435- 44.
104. Bernkop-Schnürch A, Hornof M, Zoidl T. Thiolated polymers--thiomers: synthesis and in vitro evaluation of chitosan-2-iminothiolane conjugates. Int J Pharm. 2003;266(1-2):77-82.
105. Prajapati VD, Jani GK, Moradiya NG, Randeria NP. Pharmaceutical applications of various natural gums, mucilages and their modified forms. Carbohydr Polym. 2013;92(2):1685-99.
106. Bannigan P, Aldeghi M, Bao Z, Häse F, Aspuru-Guzik A, Allen C. Machine learning in drug delivery. Annu Rev Biomed Eng. 2023;25:25.1-25.30.
107. Takayama K, Fujikawa M, Nagai T. Artificial neural network as a novel method to optimize pharmaceutical formulations. Pharm Res. 1999 Jan;16(1):1-6.
108. Beg S, Gupta A, Shadab, Akhter S, Ahmad FJ. Artificial intelligence and machine learning in precision medicine: A paradigm shift in drug delivery. J Control Release. 2022 Oct;350:744-759.
109. Shan X, Williams GR, Wu J, Tian Y, Li Z, Zhu LM. Machine learning-powered development of a floating gastroretentive drug delivery system for sustained release of metformin. Int J Pharm. 2022 Jun 10;621:121799.
110. Patil H, Kulkarni V, Majumdar S, Sharma S. Implementation of quality by design and artificial neural network for the development of gastroretentive drug delivery system. J Pharm Innov. 2020;15(4):589-600.
111. Rodríguez-Pérez R, Bajorath J. Feature Importance for Machine Learning in Drug Discovery. Mol Inform. 2020 Aug;39(8):e2000025.
112. Mendez A, Chitturi R, Purohit S, Wang Q, Wang Y, Wang J, et al. Predicting in vivo performance of oral modified-release formulations using a novel in vitro-in vivo

correlation (IVIVC) methodology driven by machine learning. J Pharm Sci. 2023 Jan;112(1):258-270.

113. Schneck K, Gieser H. The use of digital twins and in silico modeling for generic drug development. J Pharm Sci. 2022 Apr;111(4):1027-1034.
114. Wang J, Zhang Y, Arafat B, Qin X, Li L, Wang G, et al**.** Machine learning for quality-by-design of 3D printed pharmaceuticals. Int J Pharm X. 2023 Dec;5:100165.
115. Koller DM, Posch A, Hörl G, Voura C, Radl S, Urbanetz N, et al. Continuous quantitative monitoring of powder mixing dynamics by near-infrared spectroscopy. Powder Technol. 2011 Jun 10;205(1-3):87-96.
116. Gendre C, Genty M, Julien M, Boiret M, Lecoq O, Baron M, et al. Development of a real-time visual inspection system for pharmaceutical capsules. Int J Pharm. 2013 Apr 15;447(1-2):57-63.
117. Kalantar-Zadeh K, Berean KJ, Ha N, Chrimes AF, Xu K, Grando D, et al. A human pilot trial of ingestible electronic capsules capable of sensing different gases in the gut. Nat Electron. 2018;1(1):79-87.
118. Maher S, Mrsny RJ, Brayden DJ. Intestinal permeation enhancers for oral peptide delivery. Adv Drug Deliv Rev. 2016;106(Pt B):277-319.
119. Zarek M, Layani M, Cooperstein I, Sachyani E, Cohn D, Magdassi S. 4D printing: 3D printing of shape memory polymers. 3D Print Addit Manuf. 2017;4(1):13-23.
120. Trenfield SJ, Awad A, Madla CM, Hatton GB, Firth J, Goyanes A, et al. Shaping the future: recent advances of 3D printing in drug delivery and healthcare. Expert Opin Drug Deliv. 2019;16(10):1081-94.