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REVIEW ARTICLE

Recent Developments in Gastroretentive Drug Formulations: Optimizing Therapeutic Outcomes through Prolonged Gastric Retention

Amruta Nawale[1], Madan Pomaje*[1], Apeksha Rahate[1], Ashwini Patil[1], Samruddhi Padhey[1]
[1]Govindrao Nikam College of Pharmacy, Sawarde, Ratnagiri, Maharashtra 415606
*Corresponding author email: madanpomaje@gmail.com

ABSTRACT
Gastroretentive drug delivery systems (GRDDS) are a crucial innovation in oral pharmacotherapy, designed to enhance the bioavailability and efficacy of drugs that are primarily absorbed in the upper gastrointestinal tract (GIT). This review discusses the various GRDDS strategies, including floating, swelling, bioadhesive, and high-density systems, each offering unique mechanisms to prolong gastric retention and optimize drug release. The evolution of GRDDS reflects significant advancements in technology, from traditional approaches to modern formulations like in situ gels and expandable systems. The use of magnetic fields to control gastrointestinal transit and the incorporation of nanotechnology have further refined these systems, leading to better patient adherence and improved therapeutic outcomes. An in-depth understanding of the anatomical and physiological factors that affect drug absorption, such as gastric motility, pH, and enzymatic activity, is essential for GRDDS success. This review also addresses the challenges in GRDDS development, highlighting the need for more predictive in vitro and in vivo models. The integration of these advanced delivery systems signals the future of personalized medicine, providing valuable insights for researchers and clinicians.
Keywords: Gastroretentive Drug Delivery Systems (GRDDS), Bioavailability Enhancement, Gastric Retention Mechanisms, Controlled Drug Release, Nanotechnology in GRDDS

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INTRODUCTION

Oral drug delivery systems are a common option for human administration because of their high patient compliance, affordability, convenience of use, and formulation versatility. However, owing to the variability of the gastrointestinal tract, encompassing factors such as pH of the commensal flora, gastric retention time, surface area, and enzymatic activity, these systems encounter challenges characterized by limited bioavailability. Gastroretentive Drug Delivery methods (GRDDS) were developed in response to concerns that conventional drug delivery methods would not be able to resolve. Longer gastric residence length, higher therapeutic effectiveness, and adaptability for targeted distribution in the stomach are among the advantages of GRDDS. By constantly releasing the medicine until it is entirely freed from the dosage form, they can also improve controlled delivery[1].

Because of their high patient compliance, affordability, cost-effectiveness, formulation flexibility, convenience of use, and ease of storage and transportation, oral drug delivery systems are the preferred method of administering medication to humans. Lower bioavailability, however, presents a problem because of things like the diversity of commensal bacteria in the gastrointestinal system, the pH of those bacteria, and the stomach's capacity to retain dose forms. Gastroretentive medication administration Systems (GRDDS) were developed because traditional medication administration systems might not address problems with the digestive system (GIT). The advantages of these systems include longer stomach residence times, improved drug absorption, and more controlled distribution. GRDDS can be

used to effectively treat medications that have a short half-life, unstable and poor solubility at alkaline pH, local activity in the upper gut, and restricted absorption in the lower GIT[2].

Drugs that have short half-lives, unstable solubility at alkaline pH, limited absorption in the lower gastrointestinal tract, and local action in the upper intestine are efficient in eliminating Helicobacter pylori when administered with GRDDS. raft-forming, magnetic, ion-exchange, low- and high-density systems, bio/mucoadhesive, superporous hydrogel, and raft-forming are examples of formulation techniques. Quality of GRDDS is influenced by variables such as drug solubility, viscosity grade, molecular weight, and kinds of polymers used in dosage forms [3].

The present study addresses several methods to gastroretentive drug delivery systems that have emerged as the most advanced methodology in the field of controlled release and site-specific drug delivery in recent times.

Advantages of Gastro Retentive Drug Delivery System [4]

1. The bioavailability of drugs is enhanced, as demonstrated by the significantly higher bioavailability of riboflavin in CR-GRDF as compared to non-GRDF CR polymeric formulations. The degree of medication absorption is influenced by the synergistic effects of many gastrointestinal tract processes that are involved in drug absorption and transit.
2. A boost to first-pass biotransformation is given.
3. Because CR-GRDF enables prolonged medication delivery, fewer doses are required. Flip-flop pharmacokinetics, which enable a lower dosage frequency, improve patient compliance, and improve therapeutic results for medications with a short biological half-life, may be induced by this steady and progressive input from CR-GRDF.
4. Specific treatment is offered for regional illnesses of the upper gastrointestinal tract.
5. Fluctuations in drug concentration are minimized.
6. Receptor activation selectivity is increased, enabling targeted pharmacological effects dependent on the concentration of medicines activating various receptor types.
7. There is a decrease in the body's counter-activity.
8. There is an extended period of time above the critical concentration.
9. There is a reduction in harmful activities at the colon.
10. It is easier to supply drugs to precise locations.

Disadvantages of Gastro Retentive Drug Delivery System[5]

1. Not suitable for medications like phenytoin that have a low solubility in an acidic environment.
2. Unsuitable for medications susceptible to instability in an acidic milieu, such as erythromycin.
3. Medications, such as aspirin and NSAIDs, can irritate the stomach or cause sores when released gradually.
4. Drugs that show specific absorption in the colon, like corticosteroids do.
5. Medication that is absorbed uniformly throughout the gastrointestinal system, such as nifedipine and isosorbide dinitrate.
6. To maintain buoyancy and maximum performance, floating medicine delivery devices require a significant amount of fluid in the stomach.

Physiology of stomach[6]

The stomach functions distinctly in digestive physiology and anatomically comprises three segments: the fundus, body, and antrum (pylorus). The fundus and body of the proximal segment serve as a reservoir for partially digested materials, facilitating controlled storage before further processing. In the meanwhile, the antrum is crucial because it serves as the main location for mixing movements and propels motions that work as a pump to empty the stomach. Digestion involves complex motility patterns during gastric emptying, an essential process that happens in both fed and fasted stages.The stomach undergoes a series of four distinct phases of electrical activity, collectively known as the interdigestive myoelectric cycle or migrating motor complex (MMC). These cycles occur approximately every two to three hours during fasting periods and involve coordinated contractions that move through the stomach and intestine. The transition from fasting to feeding conditions, characterized by altered contraction patterns, marks the onset of digestive motility following the ingestion of a mixed meal.

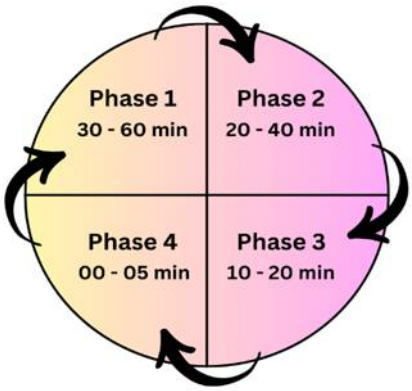

Figure-1. Motility Pattern in GIT

An essential part of digestion is played by the gastrointestinal (GI) motility stages. During the 40–60 minute Phase I (Basal phase), sporadic contractions lay the foundation for the activities that follow. The preparation phase lasts 40–60 minutes before Phase II (Preburst phase) begins with the appearance of sporadic contractions and action potentials. Phase III (Burst phase) then begins, lasting 4–6 minutes with strong, regular contractions that aid in effective digestion. Phase IV is a transitional phase that lasts from 0 to 5 minutes and occurs in between cycles of Phases III and I[7].The contraction pattern changes from the fasting to the fed state when a mixed meal is consumed. This is known as the digestive motility pattern. This rhythm reflects ongoing contractions similar to Phase II fasting, coordinating the dwindling of food particles to less than 1 mm. The digestion process is accelerated by these particles as they are driven in suspension towards the pylorus. Gastric emptying slows down in the fed state due to a delayed start of the Migrating Myoelectric Complex (MMC). Interestingly, controlled-release dose forms used orally can cause issues such as a brief gastrointestinal residency duration and an irregular gastric emptying rate, as shown by scintigraphy investigations on gastric emptying rates.

A promising medication option for a gastro-retentive drug delivery system is[8]

1. Specific enzymes, antacids, misoprostol, 5-fluorouracil, anti-reflux medications, and anti-Helicobacter pylori drugs are among the medications that have localized effects in the stomach.
2. Drugs that are mostly absorbed in the stomach.
3. Baseline medications that is acid-soluble and poorly soluble in alkaline pH, such as quinidine, salbutamol, verapamil, metoprolol, propranolol, cinnarizine, diazepam, diltiazem, and chlordiazepoxide and chlorpheniramine.
4. Medication that is quickly absorbed from the GI system.
5. Drugs that can become unstable in the lower GI tract and degrade in the colon; captopril is one such example
6. Medications that show specific absorption in the stomach or upper parts of the small intestine, such as thiamine, atenolol, piretanide, riboflavin-50-phosphate, levodopa, furosemide, and salbutamol (albuterol).
7. Medications with varying bioavailability; levodopa and sotalol hydrochloride in particular.

Drugs Unsuitable for Gastroretentive Drug Delivery System[9]

1. Pharmaceuticals exhibiting restricted solubility in acidic environments, exemplified by Phenytoin.
2. Medications susceptible to instability in the gastric milieu, illustrated by Erythromycin.
3. Drugs primarily designed for targeted release in the colon, including examples such as 5-amino salicylic acid and corticosteroids.

Table-1. Comparing GRDDS with Conventional drug delivery systems.

Sr no	Aspect	Conventional DDs	GRDDs
1	Design and Mechanism	Designed for rapid release and absorption in the GI tract.	Designed to prolong drug residence time in the stomach. Utilizes floating, bioadhesive, expandable, or mucoadhesive systems.
2	Therapeutic Benefits	Provides rapid onset of action, consistent systemic drug levels, suitable for drugs needing quick absorption.	Improves bioavailability, reduces dosing frequency, minimizes fluctuations in plasma drug levels, potentially lowers side effects.
3	Toxicity	Systemic toxicity potential if rapid	May reduce systemic toxicity by limiting drug

		absorption occurs.	exposure outside the stomach.
4	Patient compliance	Compliance may vary due to frequent dosing requirements.	May improve compliance due to reduced dosing frequency and consistent drug levels.
5	Drug Degradation in the Colon	Drugs may degrade in the colon if intended for release in the small intestine.	Protects drugs from degradation in the colon, which is beneficial for stability.
6	Dose Dumping	Risk of dose dumping if formulation integrity is compromised.	Less susceptible to dose dumping phenomenon compared to some immediate-release formulations.

APPROACHES OF GRDDS[10]

The dosage forms known as gastroretentive ones are intended to be kept in the stomach.

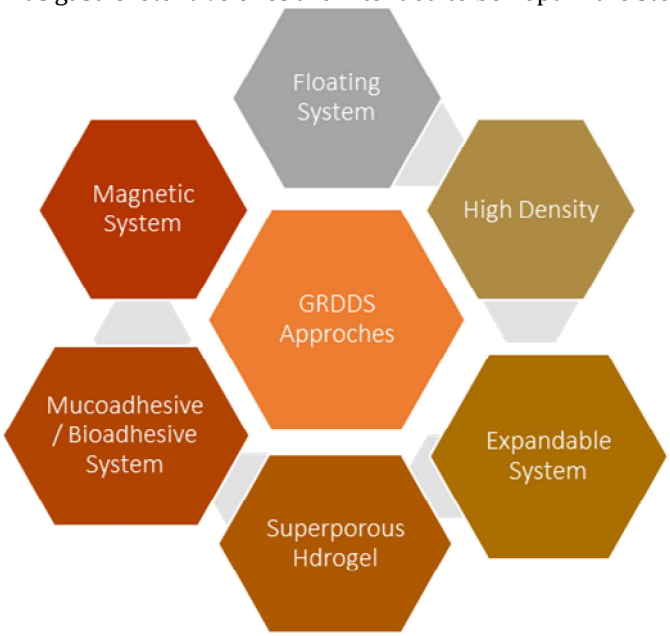

Figure-2. Approaches of GRDDS

High Density [11]

The high-density GRDDS technique promotes retention and prolonged drug release by using the dose form's weight to hold it in place in the stomach. This strategy tackles the problems associated with gastric retention and offers a dependable method for long-term medication administration, particularly for medications that need to remain in the stomach for a long time to have the best possible absorption or therapeutic impact. To increase the density of GRDDS and preserve its integrity and structure, high-density materials are utilized, such as polymers and fillers. High-density materials are frequently found in fillers and polymers. Achieving regulated and prolonged drug release is the goal of the high-density method, which is essential for drugs with particular absorption needs or those with a limited therapeutic window.

Expandable System[12]

Over the past three decades, a complex method known as Expandable Gastroretentive Drug Administration Systems (GRDDS) has been developed to increase drug administration by lengthening the stomach residence period. GRDDS, which were first created for veterinary use, are intended to extend the time that a medication is retained in the stomach, allowing for more controlled release and better treatment results. A crucial aspect of them is their expandability, which enables dosage forms to adjust to the physiological circumstances of the stomach and promotes regulated release and drug retention. In order to provide sustained contact with the stomach mucosa and facilitate medication absorption and release kinetics, GRDDS are essential, especially for drugs that have unique site-related actions in the upper gastrointestinal tract (GIT). When prolonged drug release is necessary for therapeutic effectiveness,this strategy is useful. GRDDS also tackle issues with medication release kinetics and bioavailability [13].

Mucoadhesive / Bioadhesive System [14]

Advances in pharmaceutical technology that employ specific polymers to improve drug delivery include mucoadhesive and bioadhesive systems in gastroretentive drug delivery systems. Through the interaction

of polymeric chains with mucin glycoproteins, mucoadhesive systems create a robust bond that penetrates the mucosal barrier and enables regulated medication release and enhanced bioavailability. This approach improves therapeutic effectiveness especially for medications that need to be released selectively into particular GIT areas. To provide regulated medication release, bioadhesive devices attach dosage forms to biological tissues. Precise control over the kinetics of drug release is provided by these systems, guaranteeing the best possible therapeutic results and reducing problems associated with low bioavailability and irregular drug absorption. A potential method of medication administration is the GRDDS Mucoadhesive and Bioadhesive System, which provides targeted and controlled release, enhanced bioavailability, and prolonged residence time within the GIT [15].

Magnetic System[16]

Magnetic systems are used in gastroretentive drug delivery systems to regulate the medication's release and prolong its stomach stay. The medicine is made magnetically sensitive by adding magnetic components, and its travel inside the gastrointestinal system is regulated by an external magnetic field. Utilizing magnetic resonance imaging (MRI), the in vivo drug's gastro-retention is verified. This method allows for customized treatment plans and is useful when other retention techniques are impractical. This method's magnetic system provides a comprehensive and adaptable drug delivery strategy, guaranteeing the stomach's focused and continuous release of medicinal compounds[17].

Superporous Hydrogel[18]

The degree of porosity in these very porous systems sets them apart from traditional swelling-type systems, and they have the capacity to prolong the Gastroretention Time (GRT). With an average pore size greater than 100 µm, they are distinguished by fast swelling that quickly reaches equilibrium size. The rapid swelling characteristic is dependent on the absorption of water by an openly porous material, which is triggered by capillary force. The goal is to ensure that they have enough mechanical strength to resist the pressure that is delivered during stomach contractions. This is achieved by co-forming the hydrophilic particulate material Ac-Di-Sol (croscarmellose sodium) with other components. Chitosan/poly (vinyl alcohol) has been used as an interpenetrating polymer to help construct rosiglitazone maleate, an antidiabetic medicine, into superporous hydrogels for use as a gastroretentive drug delivery system (GRDDS)[18].

Floating System[19]

Floating Drug Delivery Systems (FDDS) or Hydrodynamically Balanced Systems (HBS) are low-density formulations that are naturally inclined to float on top of stomach contents, ensuring prolonged retention. Because of this extended existence, the drug's constituent parts may be delivered under control and at a predetermined rate. These systems are vital for lengthening the duration of gastro-retention and decreasing fluctuations since they float in the stomach environment. As the driving force behind gastro-retentive drug delivery systems, FDDS regulates a medication's pharmacokinetic release kinetics by accurately delivering it to the target region in order to provide the desired pharmacological effects[20], [21].

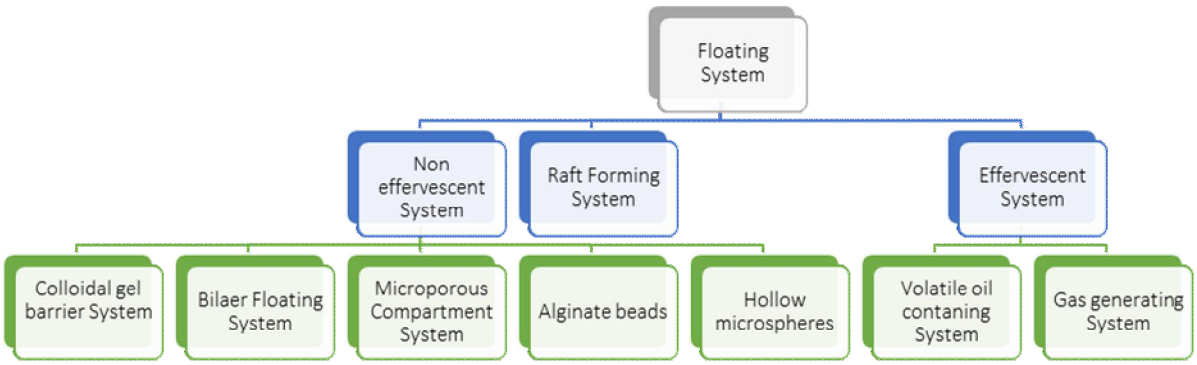

Figure-3. Floating Drug Delivery System

a. Effervescent System [22]

This system utilizes a buoyancy chamber capable of being filled with air, water, vacuum, or inert gas. You may add CO2 to the floating chamber, which is created when the carbonate and bicarbonate salts combine with the organic acid (citric acid). This type of device employs a matrix made of effervescent substances like citric acid, sodium bicarbonate, and tartaric acid, swellable polymers like chitosan-like

polysaccharides, or chambers filled with a liquid that gasifies at body temperature. This system's constituent swelling polymers include disodium glycine, citric acid, tartaric acid, and sodium bicarbonate. An effervescent material is how this composition is described. The formula becomes buoyant in the stomach because the mechanism releases carbon dioxide when it comes into touch with gastric fluid.

The optimal gas generation in this system is achieved with a specific ratio of 0.76:1 between sodium bicarbonate and citric acid. Tablets, the preferred form of this formulation, can be either divided into multiple pills or designed as a single matrix unit. Single matrix tablets may comprise one or more layers, adding complexity to the drug delivery system. Additionally, there are documented cases of floating systems employing ion exchange resins as part of the formulation. The release of drugs from both effervescent and similar systems is a crucial aspect of their functionality[23].

Gas generation system [24]

Grouped under the more general heading of effervescent systems is the gas generating system. A chemical interaction between citric acid and sodium bicarbonate releases carbon dioxide, which is how this system works. This process is known as an effervescent reaction. Since it contributes to the generation of gases, especially carbon dioxide, this effervescent reaction is essential to the system's operation.

The medication is enclosed in a hydrocolloid layer when it comes to drug administration. Changes to the drug's specific gravity and density are mostly dependent upon this layer. Specific gravity and density of the confined medication decrease when it is exposed to the effervescent reaction that releases carbon dioxide. The medication therefore becomes buoyant and is able to float above the stomach contents when the gases produced during the effervescent phase are released[25].

This phenomenon, as elucidated by Raza et al. in the World Journal of Pharmacy and Pharmaceutical Sciences, Volume 11, Issue 9 (2022), introduces a dynamic interplay between the effervescent reaction, drug encapsulation in a hydrocolloid layer, and the subsequent alteration of drug properties to achieve controlled and targeted drug delivery.

Volatile oil containing system

To improve medication retention in the stomach, precise design goes into the creation of gastroretentive drug delivery devices that include an inflatable chamber. The two integrated chambers make up this inventive arrangement. While the secondary chamber holds a volatile liquid, such ether or cyclopentane, the primary chamber holds the medicinal medication.

The critical mechanism involves the gasification of this volatile liquid at body temperature. This transformative process induces inflation of the inflatable chamber within the gastric environment.

The gasification of the liquid occurs in response to the physiological conditions of the stomach, triggering the expansion of the inflatable chamber. This inflation contributes to the sustained retention of the drug delivery system within the gastric region. The utilization of cyclopentane or ether as volatile liquids ensures a controlled and targeted response, aligning with the desired drug release profile.

This advanced design, elucidated in various academic sources including studies by Tripathi et al. and Lodh et al., signifies a promising avenue in pharmaceutical research for optimizing drug delivery and therapeutic outcomes[26].

Non-Effervescent FDDS[27]

The internal workings of polymer-based processes, including polymer swelling or bioadhesion to the mucosal layer, provide the foundation for the performance of non-effervescent Floating Drug Delivery Systems (FDDS) in the gastrointestinal (GI) tract. Improved medication retention and controlled release in the GI environment are the goals of this focused strategy.

The key excipients integral to non-effervescent FDDS formulations encompass a diverse array of materials carefully selected for their specific properties:

Hydrophilic Gums: These polymers exhibit a high affinity for water, facilitating rapid hydration and subsequent swelling, contributing to the buoyancy of the drug delivery system. Gel-Forming or Highly Swellable Cellulose Type Hydrocolloids: Cellulose derivatives with exceptional swelling capabilities play a pivotal role in sustaining the floatation of the drug delivery system within the GI tract[28].Polysaccharides: Natural polymers like polysaccharides contribute to the overall matrix structure, aiding in the controlled release of the drug payload.Matrix-Forming Materials: This category encompasses synthetic materials such as polymethacrylate, polycarbonate, polystyrene, and polyacrylate. These matrix-forming materials play a crucial role in maintaining the structural integrity and controlled drug release characteristics of the system.

Bioadhesive Polymers: Bioadhesive polymers such as Carbopol and Chitosan significantly contribute to mucosal adhesion, thereby prolonging the residence time of the drug delivery system in the gastrointestinal tract. This combination of excipients underscores the sophisticated design and

therapeutic potential of non-effervescent FDDS, offering a promising avenue for targeted and controlled drug delivery in gastrointestinal applications.

Colloidal gel barrier systems / Single layer floating tablets[29]

The described pharmaceutical approach employs a strategic method to enhance the bioavailability of drugs by extending their stomach retention time, thereby promoting increased absorption in solution form at the targeted site. This methodology primarily involves the amalgamation of a therapeutic agent with gel-forming hydrocolloids to establish buoyancy within the gastric environment.

The formulation includes gel-forming cellulose-type hydrocolloids, such as hydroxypropyl methylcellulose (HPMC), polysaccharides, and matrix-forming polymers like polycarbophil, polystyrene, and polyacrylate. These hydrocolloids are chosen for their ability to interact with gastrointestinal (GI) fluid through hydration, crucially maintaining the drug's buoyancy within the system.

The hydration process initiates the formation of a colloidal gel barrier that encapsulates the drug, creating a protective hurdle within the GI tract. This barrier serves to prolong the stomach retention time of the drug, facilitating sustained release and optimal absorption. The orchestrated interaction between the drug and the gel-forming hydrocolloids underscores a sophisticated pharmaceutical strategy aimed at optimizing therapeutic outcomes through controlled and targeted drug delivery

Bi-layer floating tablets[30]

One kind of pharmaceutical formulation having a dual-layer structure is the bi-layer floating tablet. The sustained release layer forms an impenetrable colloidal gel barrier by interacting with stomach fluid, while the immediate release layer releases the medication's principal dosage. The tablet's buoyancy in the stomach environment is improved by this barrier. The buoyant properties of the sustained release layer depend on its capacity to sustain a bulk density of less than 1. For increased therapeutic efficacy, this design maximizes drug release kinetics, guaranteeing both instantaneous release and prolonged drug release duration[31], [32].

Microporous compartment systems[33]

To ensure that particles of undissolved medication do not come into contact with the stomach surface, the drug delivery system uses a microporous compartment that is sealed on both the top and bottom. The flotation chamber, which is made up of trapped air, helps the stomach stay buoyant.

The medicine may dissolve under control thanks to the microporous architecture, which permits stomach fluid to pass through the opening. A prolonged release of the dissolved medication is ensured by the outer seal, which shields undissolved drug components from the stomach lining. This system makes sure the medication gets throughout the intestines and into the body continuously[34].

Alginate Beads[35]

Pharmaceutical manufacture has employed freeze-dried calcium alginate to produce floating dosage forms with multiple units. A sodium alginate solution and an aqueous calcium chloride solution are combined to create these 2.5 mm diameter spherical beads. Consequently, the precipitation of calcium alginate confers a porous structure to the beads.

The developed floating beads demonstrate the efficacy of the porous system, exhibiting a significantly prolonged residence period exceeding 5.5 hours. The porosity induced by calcium alginate precipitation enhances stomach retention duration, thereby facilitating sustained drug release and enhancing therapeutic efficacy. This extended residence time is crucial in pharmaceutical design as it enables continuous drug release and improves therapeutic outcomes.

Micro balloons / Hollow microspheres

To increase shelf life and gastrointestinal retention time (GRT), drug-containing microspheres are being developed for pharmaceutical formulations. These microspheres are made of polymers such as polycarbonate, cellulose acetate, calcium alginate, Eudragit S, low methoxy agar, and pectin. These microspheres have certain characteristics including regulated medication release and longer retention throughout the gastrointestinal system. For more than 12 hours, these small hollow spheres were let to float continually over an acidic surfactant hydrolysis solution in order to evaluate their durability and effectiveness. These tiny hollow spheres have the potential to be effective medication delivery devices, as evidenced by their extended floating capabilities. Pharmaceutical research is currently pointing to these small hollow spheres as a novel way to combine the benefits of a multi-module drug delivery system with remarkable buoyancy.

Raft-forming systems[36]

In cases of gastroesophageal reflux disease and other gastrointestinal diseases, raft-forming mechanisms are useful for delivering antacids. Upon contact with gastrointestinal fluid, these systems undergo gelation, forming a cohesive and viscous gel. When this gel, which is composed of sodium alginate and calcium carbonate, comes into touch with the fluid, it forms a continuous layer known as a raft. When

calcium ions and sodium alginate combine, a low-density gel is created that floats and takes the shape of a barrier on the digestive fluid. For buoyancy, NaHCO3 can also be utilized. Diffusion, swelling, and cross-linking make up the physical mechanism of the system, whereas pH and temperature-dependent swellings dominate its physiological stimulation. In these systems, polymers such as gellan gum, chitosan, carbopol, and alginic acid are used[37].

PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS OF FDDS

Pharmacokinetics aspects of FDDS

Absorption window[38]

This article examines many experimental methods for validating medications classified as agents with a restricted absorption window. Through close examination of the test compound's absorption characteristics, these methods provide light on the dynamics of intestinal permeability and absorption in various gastrointestinal tract areas. The review describes the several approaches taken to investigate these characteristics, exposing the complex mechanisms controlling intestinal absorption and investigating differences in permeability within certain GI tract segments[39].

Enhanced bioavailability[40]

Exploration of bioavailability enhancement strategies for compounds exhibiting a limited absorption window involves continuous targeted administration to optimize bioavailability. For instance, certain bisphosphonates like alendronate demonstrate direct absorption from the stomach region, highlighting the potential benefits of sustained gastric delivery to enhance bioavailability[41].

Enhanced first pass biotransformation:

Enhancing pre-systemic metabolism through sustained drug administration demonstrates notable effects on metabolic enzymes, particularly cytochrome P450, notably CYP3A4. Continuous administration contrasts with bolus inputs, aligning with improved efficacy observed in active transporters with capacity-limited activity.

Enhanced bioavailability resulting from decreased P-glycoprotein (P-gp) activity in the duodenum

Pgp mRNA levels are shown to increase longitudinally across the gut, with the colon having the highest levels. This is in contrast to the upper region of the intestine having a higher density of CYP3A4. As P-gp substrates that do not experience oxidative metabolism, floating systems may therefore improve absorption relative to the immediate and CR dosage forms for drugs like digoxin[42].

Reduced frequency of dosing[43]

Continuous and gradual administration via a controlled-release floating system may induce flip-flop pharmacokinetics, potentially reducing dosing frequency for drugs with short biological half-lives. This characteristic is linked to increased patient compliance, thereby enhancing overall therapy effectiveness.

Targeted treatment for regional illnesses in the upper gastrointestinal tract:

The sustained and uninterrupted delivery of medication from floating systems to the stomach offers potential benefits for localized therapy in the gastric and small intestinal regions.

PHARMACODYNAMIC CONSIDERATIONS OF FDDS:

Minimized drug concentration variability:

When medications are administered continuously via floating systems, the blood drug concentrations that are produced have a narrower range than with formulations that are released immediately. This approach reduces concentration-dependent adverse responses associated with peak concentrations by successfully mitigating oscillations in medication effects. This characteristic takes on more importance for medications with a limited therapeutic index. Moreover, a higher level of selectivity in receptor activation is made possible by the carefully planned decrease in drug concentration variations. Some pharmacological effects can be elicited thanks to this modulation, particularly when medications activate distinct receptor types at various concentration thresholds.

Minimization of adverse effects in the colon[44]

By retaining the drug within the gastroretentive drug delivery system (GRDF) in the stomach, the amount reaching the colon is restricted. This approach potentially mitigates undesirable effects of the medication on the colon. This pharmacological attribute underscores the rationale for formulating beta-lactam antibiotics in a floating formulation, as they are absorbed exclusively from the small intestine, and their presence in the colon can foster bacterial growth.

Evaluation of GRFDDS

Angle of Repose[45]

The resistance forces experienced by loose grains or powder can be quantified using the angle of repose, which represents the maximum angle achievable between the surface of a pile of grains or powder and

the horizontal plane. Granules were allowed to flow freely through a funnel positioned at a fixed height (h) attached to a platform. The angle of repose was subsequently determined by measuring the radius and height of the granule heap formed.

$$\tan\theta = h/r$$

In this case, θ represents the angle of repose, h stands for heap height, and r for heap radius.

compressibility index[46]

To assess the flow properties of a powder, one can evaluate its bulk density (ρo) and tapped density (ρt), which indicate how densely the powder packs under specific conditions.

Applying the equation

Compressibility index (%)=ρt−ρ0/ρtx100,

In this case, ρ0 = Bulk density g/ml002E and ρt = tapped density g/ml

Post-compression parameters:

Shape of Tablet[47]

A magnifying lens was used to examine compressed pills for tablet form. To measure the diameter and thickness, we utilized a graduated varnier caliper. The thickness of each tablet was measured after we arbitrarily picked three of each formulation.

Hardness [48]

The hardness of tablets indicates their resistance to mechanical shocks during handling. Tablet hardness was assessed using a Monsanto hardness tester, with measurements reported in kg/cm^2. Three tablets chosen at random were tested to determine their hardness.

Friability[49]

Roche Friabilator was utilized to determine the level of friability in the tablets. The percentage (%) used to express it was used. Ten pills were initially put into a friabilator after being weighed (W initial). For four minutes, or up to 100 rotations, the friabilator was run at 25 rpm. Wfinal was the weight of the pills once more. After that, the percentage was determined using the formula:

% of Friability = 100 (1-W0/W) %

It was deemed acceptable for tablets with less than 1% friability.

Density of tablets[50]

Tablet density was a critical consideration for floating tablets, as buoyancy would occur only if the tablet's density was lower than that of stomach fluid (1.004 g/cm^3). The tablet density was determined using the following relationship.

$$V = r2h\ d = m/v$$

In this case, v stands for tablet volume (cc), r for tablet radius (cm), h for tablet crown thickness (g/cc), and m for tablet mass.

Test for Weight Variation[51]

From each batch, 10 tablets were randomly selected and individually weighed to detect variations in weight. The weight variability of tablets was within permissible limits set by the U.S. Pharmacopoeia, which allows for specific percentage fluctuations in weight.

Calculation of buoyancy lag time[52]

Tablet buoyancy, characterized by the buoyancy lag time, refers to the period it takes for a tablet to float and reach near the surface. At a controlled temperature of 37±0.5ºC, tablets were assessed in 900 millilitres of simulated stomach fluid. The entire duration of tablet floating was visually observed, and the buoyancy lag time was determined using a stopwatch.

Floating time[53]

The USP Dissolution Apparatus-II was employed to evaluate floating characteristics in 900 ml of 0.1N HCl at 50 rpm, maintaining a constant temperature of 37±0.5ºC. The duration for which the tablet remains buoyant in the dissolution medium, encompassing the floating lag time (the time taken for the tablet to ascend to the surface), was observed visually. This duration is referred to as the floating time.

Swelling Index[54]

A swelling analysis was performed on tablets containing a sustained-release floating layer. Each tablet was accurately weighed and placed in USP Dissolution Apparatus II, where they swelled until reaching a constant weight. The apparatus contained 900 ml of 0.1N HCl maintained at 37±2ºC. After removing the tablets, any weight variances were recorded and excess liquid blotted using filter paper. Each experiment was conducted in triplicate. Subsequently, the swelling index was determined using this method.

Drug Content[55]

Five tablets from a batch were randomly chosen, weighed, and ground into powder using a mortar. A precisely measured amount of this powdered tablet material, equivalent to 100 mg, was added to a

standard flask filled with 0.1 N HCl up to the brim. The mixture was subsequently filtered through a 0.45 µm membrane filter paper. Analysis was then performed using spectrophotometric techniques.

In-vitro dissolving studies[56]

The release rate of floating tablets was evaluated using the USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed at 37 ± 0.5°C using 900 milliliters of 0.1N HCl. At hourly intervals over a period of twelve hours, five milliliters of the dissolution medium were withdrawn from the apparatus. Each withdrawn sample was immediately replaced with fresh dissolution medium. The absorbance of these samples was measured after filtration through Whatman filter paper[57].

Application of FDDS[58]

Extended Drug Release: FDDS is able to provide medications that need to be released gradually over time or that have a short half-life. The dose form stays in the gastrointestinal tract for a longer period of time by float on the gastric contents. Increased Bioavailability: FDDS can be used to manufacture drugs that are intended to dissolve slowly, which improves absorption and bioavailability. This is especially useful for drugs with low permeability or poor solubility. This is crucial for medications whose solubility in water is low. Drug Delivery through Gastroretentive Forms: FDDS can be used to create dosage forms that are able to stay in the gastrointestinal tract for a longer amount of time, increasing the absorption of the drug and its therapeutic effect. This is helpful for medications that have windows of absorption in the upper small intestine or stomach. Treatment of Gastrointestinal Disorders: Helicobacter pylori infections, peptic ulcers, and gastroesophageal reflux syndrome can all be treated with medications delivered by FDDS. FDDS can improve local concentrations of drugs at the site that acts by extending the drug's residence duration in the stomach, which can improve therapeutic results.

Targeted Drug Delivery: For targeted drug delivery, FDDS can be made to specifically target parts of the digestive system, like the gastrointestinal tract or upper small intestine. By doing this, the medication's therapeutic index can be raised and systemic side effects can be reduced[59]. Chronotherapy: Drugs are released into the body at a certain time of day to align with the body's biological cycles. FDDS can be used for this type of medication administration. This is especially important for conditions where symptoms change over the day or when precise times are needed for maximum drug concentrations. Combination treatment: FDDS can be used to administer several medications at once, either in discrete dosage forms or in fixed-dose combinations. This makes it possible to administer medications with various physicochemical profiles or mechanisms simultaneously[60].

Recent advancements of GRDDS

Gastroprotective drug delivery systems (GRDDS) have witnessed significant advancements in recent years, contributing to improved drug delivery efficiency and patient compliance. Several notable advancements include: Novel Formulation Techniques: Recent research has focused on developing novel formulation techniques to enhance gastric retention. This includes the use of polymers with mucoadhesive properties, such as chitosan and alginate, to prolong residence time in the stomach[61]. Innovative Drug Release Mechanisms: Advanced drug release mechanisms, such as swellable, floating, and expandable systems, have been explored to prolong drug release and improve bioavailability. These mechanisms utilize gas-generating agents or swelling agents to achieve buoyancy and enhance gastric retention. Nanotechnology Applications: Nanomaterials have emerged as promising tools in GRDDS development. Nanoparticles, liposomes, and nanoemulsions offer enhanced drug solubility, stability, and targeted delivery, thereby improving therapeutic outcomes. Incorporation of Stimuli-Responsive Components: GRDDS incorporating stimuli-responsive components, such as pH-sensitive polymers or magnetic nanoparticles, enable controlled drug release triggered by physiological changes in the gastrointestinal tract. This ensures site-specific drug delivery and optimized therapeutic effects. Advanced Characterization Techniques: Utilization of advanced characterization techniques, including imaging studies and computational modeling, facilitates better understanding of GRDDS behavior in vivo. This aids in optimizing formulation parameters and predicting drug release kinetics [62]. Personalized Medicine Approaches: Integration of personalized medicine concepts into GRDDS design allows for tailored drug delivery based on individual patient characteristics, such as gastric emptying rate and gastrointestinal physiology. This enhances treatment efficacy while minimizing adverse effects.

CONCLUSION

The reviewed literature underscores the pivotal role of gastroprotective drug delivery systems (GRDDS) in revolutionizing oral drug administration. It delves into the intricate interplay between anatomical and physiological factors governing gastric retention, shedding light on formulation intricacies and recent strides in GRDDS innovation. These strides encompass a spectrum of breakthroughs, ranging from pioneering formulation methodologies to cutting-edge drug release mechanisms and the integration of

nanotechnology. Moreover, the incorporation of stimuli-responsive elements and the application of advanced characterization methodologies herald a new era of precision medicine within the GRDDS domain. Collectively, these advancements herald a promising trajectory towards augmenting drug bioavailability, protracting gastric residence duration, and refining drug targeting precision, thus culminating in superior therapeutic outcomes

REFERENCES

1. S. More, K. Gavali, O. Doke, and P. Kasgawade, (2018). "Gastroretentive Drug Delivery System," *Journal of Drug Delivery and Therapeutics*, vol. 8, no. 4, doi: 10.22270/jddt.v8i4.1788.
2. C. M. Lopes, C. Bettencourt, A. Rossi, F. Buttini, and P. Barata, (2016). "Overview on gastroretentive drug delivery systems for improving drug bioavailability," 23, *Elsevier B.V.* doi: 10.1016/j.ijpharm.2016.05.016.
3. M. J Bhandwalkar, P. S Dubal, A. K.Tupe, and S. N Mandrupkar,(2020). "Review On Gastroretentive Drug Delivery System," *Asian Journal of Pharmaceutical and Clinical Research*, pp. 38–45. doi: 10.22159/ajpcr.2020.v13i12.37264.
4. Streubel, A., Siepmann, J., & Bodmeier, R. (2006). Gastroretentive drug delivery systems. *Expert Opinion on Drug Delivery*, *3*(2), 217–233. https://doi.org/10.1517/17425247.3.2.217
5. V. K. Pawar, S. Kansal, G. Garg, R. Awasthi, D. Singodia, and G. T. Kulkarni,(2011). "Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems,. doi: 10.3109/10717544.2010.520354.
6. S. R. Chaudhry, M. N. P. Liman, and D. C. Peterson, "Anatomy, Abdomen and Pelvis: Stomach," *StatPearls*, Oct. 2022, Accessed: Aug. 31, 2023. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK482334/
7. S. Shah, R. Qaqish, V. Patel, and M. Amiji, (1999). "Evaluation of the factors influencing stomach-specific delivery of antibacterial agents for Helicobacter pylori infection," *J Pharm Pharmacol*, vol. 51, no. 6, pp. 667–672. doi: 10.1211/0022357991772952.
8. C. S. Murphy, V. Pillay, Y. E. Choonara, and L. C. Du Toit, (2009). "Gastroretentive Drug Delivery Systems: Current Developments in Novel System Design and Evaluation," Current Drug Delivery. 6[5]: 451-460.
9. A. I. Badoni, A. Ojha, G. I. Gnanarajan, and P. I. Kothiyal, (2012). "Review on Gastro Retentive Drug Delivery System," The Pharma Innovation: Vol. 1, [8], 20-26. [Online]. Available: www.thepharmajournal.com
10. P. Patrojanasophon, T. Charoenying, and P. Opanasopit, (2023). "Gastroretentive drug delivery approaches: concepts, approaches, and applications," *Advanced and Modern Approaches for Drug Delivery*, pp. 77–90. doi: 10.1016/B978-0-323-91668-4.00022-8.
11. S. Vasa and D. Banji, "(2010). Approaches For Gastrotentive Drug Delivery Systems", IJABPT Vol 1[2]: 1-13.
12. E. A. Klausner, E. Lavy, M. Friedman, and A. Hoffman, "Expandable gastroretentive dosage forms," Jun. 24, 2003, *Elsevier*. doi: 10.1016/S0168-3659(03)00203-7.
13. M. Uboldi, A. Chiappa, M. Rossi, F. Briatico-Vangosa, A. Melocchi, and L. Zema, (2024). "Development of a multi-component gastroretentive expandable drug delivery system (GREDDS) for personalized administration of metformin," *Expert Opin Drug Deliv*, vol. 21, no. 1, pp. 131–149: doi: 10.1080/17425247.2023.2294884.
14. H. Patil, R. V. Tiwari, and M. A. Repka, (2016)."Recent advancements in mucoadhesive floating drug delivery systems: A mini-review," *Editions de Sante*. doi: 10.1016/j.jddst.2015.12.002.
15. V. V. Khutoryanskiy, "Advances in Mucoadhesion and Mucoadhesive Polymers," *Macromol Biosci*, vol. 11, no. 6, pp. 748–764, Jun. 2011, doi: 10.1002/mabi.201000388.
16. F. Sharifianjazi *et al.*, "Polymer incorporated magnetic nanoparticles: Applications for magnetoresponsive targeted drug delivery," *Materials Science and Engineering: B*, vol. 272, p. 115358, Oct. 2021, doi: 10.1016/J.MSEB.2021.115358.
17. R. Ito, Y. Machida, T. Sannan, and T. Nagai, "Magnetic granules: a novel system for specific drug delivery to esophageal mucosa in oral administration," *Int J Pharm*, vol. 61, no. 1–2, pp. 109–117, Jun. 1990, doi: 10.1016/0378-5173(90)90049-A.
18. Alqahtani MS, Kazi M, Alsenaidy MA, Ahmad MZ. (2021). Advances in Oral Drug Delivery. Front Pharmacol. 19;12:618411. doi: 10.3389/fphar.2021.618411. PMID: 33679401; PMCID: PMC7933596.
19. Kotreka UK, Adeyeye MC. (2011). Gastroretentive floating drug-delivery systems: a critical review. Crit Rev Ther Drug Carrier Syst. 28(1):47-99. doi: 10.1615/critrevtherdrugcarriersyst.v28.i1.20. PMID: 21395515.
20. G., Yashavanth & Goudanavar, Prakash & T., Mallamma. (2022). Floating Drug Delivery System: A Review. International Journal of Advanced Research. 10. 161-167. 10.21474/IJAR01/15653.
21. S. Sneha, V. Trupti, A. D. (2015). "A review: Floatable gastroretentive drug delivery system," *indianjournals.com*, Accessed: Jul. 25, 2024. [Online]. Available: https://www.indianjournals.com/ijor.aspx?target=ijor:ajp r& volume=5&issue=1&article=008
22. B. A. Daihom, E. Bendas, M. I. Mohamed, B. A. Daihom, E. R. Bendas, and A. A. Badawi, (2020). "Development and in vitro evaluation of domperidone/Dowex resinate embedded gastro-floatable emulgel and effervescent alginate beads," *Elsevier*, doi: 10.1016/j.jddst.2020.101941.
23. S. S. Badve, P. Sher, A. Korde, and A. P. Pawar, (2007). "Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 65, no. 1, pp. 85–93. doi: 10.1016/j.ejpb.2006.07.010.
24. S. H. Shaha *et al.*, (2009). "Gastro-retentive floating drug delivery system," Available: https://www.researchgate.net/ publication/266456237

25. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y. (1992). Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci. 81(2):135-40. doi: 10.1002/jps.2600810207. PMID: 1372046.
26. R. Kumar and A. Philip, (2007). "Gastroretentive dosage forms for prolonging gastric residence time," *International Journal of Pharmaceutical Medicine*, vol. 21, no. 2, pp. 157–171. doi: 10.2165/00124363-200721020-00005.
27. S. Kumar Vishwakarma, J. N. Mishra, and D. Kumar Vishwakarma, (2021). "A Review on GRDDS Recent Advances In Drug Delivery Systems And Its Application," *wjpr.s3.ap-south-1.amazonaws.com*, vol. 10, no. 11, p. 1159.doi: 10.20959/wjpr202111-21554.
28. S. Kim, K. M. Hwang, Y. S. Park, T. T. Nguyen, and E. S. Park, (2018). "Preparation and evaluation of non-effervescent gastroretentive tablets containing pregabalin for once-daily administration and dose proportional pharmacokinetics," *Int J Pharm*, vol. 550, no. 1–2, pp. 160–169. doi: 10.1016/j.ijpharm.2018.08.038.
29. S. Thakur, B. Sharma, A. Verma, J. Chaudhary, S. Tamulevicius, and V. K. Thakur, (2018). "Recent progress in sodium alginate based sustainable hydrogels for environmental applications," *J Clean Prod*, vol. 198, pp. 143–159. doi: 10.1016/J.JCLEPRO.2018.06.259.
30. M. A. El Nabarawi, M. H. Teaima, R. A. A. El-Monem, N. A. El Nabarawy, and D. A. Gaber, (2017). "Formulation, release characteristics, and bioavailability study of gastroretentive floating matrix tablet and floating raft system of Mebeverine HCl," *Drug Des Devel Ther*, vol. 11, pp. 1081–1093. doi: 10.2147/DDDT.S131936.
31. T. Maria Stanley, P. R. Raj, (2007). "Formulation and evaluation of floating beads of esomeprazole magnesium USP," *International Journal of Pharmaceutical Chemistry and Analysis*, vol. 6, no. 2, p. 40, doi: 10.18231/j.ijpca.2019.007.
32. W. He, Y. Li, R. Zhang, Z. Wu, and L. Yin, (2014). "Gastro-floating bilayer tablets for the sustained release of metformin and immediate release of pioglitazone: Preparation and in vitro/in vivo evaluation," *Int J Pharm*, vol. 476, no. 1, pp. 223–231.doi: 10.1016/j.ijpharm.2014.09.056.
33. P. Prinderre, C. Sauzet, and C. Fuxen,(2011). "Advances in gastro retentive drug-delivery systems," doi: 10.1517/17425247.2011.592828.
34. S. Arora, J. Ali, A. Ahuja, R. K. Khar, and S. Baboota, (2005). "Floating drug delivery systems: A review," *AAPS PharmSciTech*, vol. 6, no. 3, pp. E372–E390. doi: 10.1208/PT060347/METRICS.
35. S. Patel, C. Aundhia, A. Seth, N. Shah, K. Pandya, and D. Patel, (2016). "Microsponge: a novel approach in gastro-retention drug delivery system (GRDDS)," [Online]. 30-35
36. F. C. Hampson *et al.*, "Alginate-antacid combinations: Raft formation and gastric retention studies," *Drug Dev Ind Pharm*, vol. 36, no. 5, pp. 614–623, May 2010, doi: 10.3109/03639040903388290.
37. V. D. Prajapati, G. K. Jani, T. A. Khutliwala, and B. S. Zala, "Raft forming system—An upcoming approach of gastroretentive drug delivery system," *Journal of Controlled Release*, vol. 168, no. 2, pp. 151–165, Jun. 2013, doi: 10.1016/J.JCONREL.2013.02.028.
38. V. D. Prajapati, G. K. Jani, T. A. Khutliwala, and B. S. Zala, "Raft forming system - An upcoming approach of gastroretentive drug delivery system," *Journal of Controlled Release*, vol. 168, no. 2, pp. 151–165, Jun. 2013, doi: 10.1016/J.JCONREL.2013.02.028.
39. M. Ibrahim, Y. W. Naguib, H. A. Sarhan, and H. Abdelkader, "Gastro-retentive oral drug delivery systems: a promising approach for narrow absorption window drugs," J. Adv. Biomed. & Pharm. Sci. 2 (2019) 98-111
40. K. Thakar, G. Joshi, and K. K. Sawant, "Bioavailability enhancement of baclofen by gastroretentive floating formulation: Statistical optimization, in vitro and in vivo pharmacokinetic studies," *Drug Dev Ind Pharm*, vol. 39, no. 6, pp. 880–888, Jun. 2013, doi: 10.3109/03639045.2012.709249.
41. C. M. Lopes, C. Bettencourt, A. Rossi, F. Buttini, and P. Barata, (2016). "Overview on gastroretentive drug delivery systems for improving drug bioavailability," *Int J Pharm*, vol. 510, no. 1, pp. 144–158.doi: 10.1016/J.IJPHARM.2016.05.016.
42. Vijayasundiram, Kamalakannan & Puratchikody, Ayarivan & Prasanth, Viswanadhan & Masilamani, Krishnamoorthi. (2011). Enhancement of Drugs Bioavailability by Floating Drug Delivery System – A Review. International Journal of Drug Delivery. 3. 558-570.
43. R. Kumar, A. P.-I. J. of P. Medicine, "Gastroretentive dosage forms for prolonging gastric residence time," *Springer*, Accessed: Jul. 25, 2024. [Online]. Available: https://link.springer.com/article/10.2165/00124363-200721020-00005
44. Yashpal Singh Chauhan, Udichi Kataria, Ashok Dashora. (2018). Importance of Floating Drug Delivery System. Res. J. Pharm. Dosage Form. & Tech. 10(4): 220-232. doi: 10.5958/0975-4377.2018.00034.4
45. O. Macho *et al.*,(2020). "Analysis of static angle of repose with respect to powder material properties," *ojst2.is.cvut.cz*, vol. 60, no. 1, pp. 73–80. doi: 10.14311/AP.2020.60.0073.
46. C. E. Ruegger and M. Çelik, (2000). The influence of varying precompaction and main compaction profile parameters on the mechanical strength of compacts," *Pharm Dev Technol*, vol. 5, no. 4, pp. 495–505. doi: 10.1081/PDT-100102033.
47. M. Niharika, K. Krishnamoorthy, M. A.-I. J. A. Pharm, (2018). "Overview on floating drug delivery system," *researchgate.net*. doi: 10.22159/ijap.2018v10i6.28274.
48. R. Bushra, M. Shoaib, N. Aslam, … D. H.-Pak. J. P., (2024). "Formulation development and optimization of ibuprofen tablets by direct compression method," *academia.edu*, Accessed: [Online]. Available: https://www.academia.edu/download/33376110/Paper-6.pdf

49. I. Sinka, F. Motazedian, A. Cocks, K. P.-P. Technology, (2024). "The effect of processing parameters on pharmaceutical tablet properties," *Elsevier*,[Online]. Available: https://www.sciencedirect.com /sciencearticle /pii/S0032591008001976
50. M. Jayswal *et al.*, (2022). "Formulation, Evaluation and Optimization of Orodispersible Tablets of Naproxen sodium by using Superdisintegrant View project Formulation and Evaluation of Orodispersible tablets of Nifedipine 10 mg .*World Journal of Pharmacy and Pharmaceutical Sciences*, vol. 11, no. 9, doi: 10.20959/wjpps 20229-23130.
51. M. S. Reddy, (2017). "Formulation and Evaluation Of Lamivudine Sustained Release Matrix Tablets Using Jackfruit Seed Extract As Release Retardant," *World J Pharm Pharm Sci*, pp. 1050–1062.doi: 10.20959/ WJPPS20174-8793.
52. C. Kiran, C. G.-M. T. Proceedings, (2024). "Development and evaluation of interpenetrating polymer network based superporous hydrogel gastroretentive drug delivery systems (SPH IPN-GRDDS)," *Elsevier*, Accessed: Jul. 25. [Online]. Available: https://www.sciencedirect.com /science/article /pii/S2214785321014954
53. Y. Liang, W. Cheng, L. Chen, M. Sheu, H. L.(2023). Pharmaceutics, "Development of a Swellable and Floating Gastroretentive Drug Delivery System (sfGRDDS) of Ciprofloxacin Hydrochloride," *mdpi.com*, 2023, doi: 10.3390/pharmaceutics15051428.
54. Y. Mehmood *et al.*, (2014). "Swelling system of GRDDs: A novel move towards gastroretentive drug delivery system," *ijcps.com*, vol. 5, no. 2, Accessed: Jul. 25, 2024. [Online]. Available: https://www.ijcps.com/files /vol5issue2/6.pdf
55. R. Gunda, A. V.-J. P. Res, (2024). "Formulation development and evaluation of gastro retentive drug delivery systems-a review," *academia.edu*,Available: https://www.academia.edu /download/ 53846422/final-file-58ddc0a3ba2097.92335779.pdf
56. J. Ali *et al.*, (2007). "Formulation and development of hydrodynamically balanced system for metformin: In vitro and in vivo evaluation," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 67, no. 1, pp. 196–201. doi: 10.1016/j.ejpb.2006.12.015.
57. I. A. El-Said, A. A. Aboelwafa, R. M. Khalil, and O. N. Elgazayerly, "Baclofen novel gastroretentive extended release gellan gum superporous hydrogel hybrid system: In vitro and in vivo evaluation," *Drug Deliv*, vol. 23, no. 1, pp. 101–112, Jan. 2016, doi: 10.3109/10717544.2014.905654.
58. S. Mandal *et al.*, (2015). "Floating Drug Delivery System (Fdds): Types, Advantages, Disadvantages & Approaches," European Journal Pharmaceutical and Medical Research 9(3):321-326
59. E. V. Blynskaya, S. V. Tishkov, V. P. Vinogradov, K. V. Alekseev, A. I. Marakhova, and A. A. Vetcher, (2022). "Polymeric Excipients in the Technology of Floating Drug Delivery Systems," *Pharmaceutics 2022, Vol. 14, Page 2779*, vol. 14, no. 12, p. 2779. doi: 10.3390/Pharmaceutics14122779.
60. S. B. Rani, V. B. Hari, B. ReddyA, P. Devi, and V. Rajamanickam, (2013). "The Recent Developments On Gastric Floating Drug Delivery Systems: An Overveiw," *International Journal of PharmTech Research CODEN*, vol. 2, no. 1, pp. 524–534.
61. S. Raghuvanshi, K. P.-J. (2014). "Recent advances in delivery systems and therapeutics of cinnarizine: a poorly water soluble drug with absorption window in stomach," *Wiley Online Library*, vol. 2014, pp. 1–15. doi: 10.1155/2014/479246.
62. J. Jiménez-Luna, F. Grisoni, N. W. (2021). "Artificial intelligence in drug discovery: recent advances and future perspectives," *Taylor & Francis*, vol. 16, no. 9, pp. 949–959, doi: 10.1080/17460441.2021. 1909567.