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Gastroretentive Drug Delivery Systems: Innovative Strategies for Enhanced Gastric Retention and Improved Oral Drug Absorption

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ABSTRACT

Oral drug delivery is the preferred route of administration due to its convenience and patient compliance. However, it encounters limitations such as poor solubility, intestinal instability, and incomplete absorption resulting from rapid gastrointestinal transit. Gastroretentive drug delivery systems (GRDDS) have emerged as a strategy to address these challenges by prolonging gastric residence time and enhancing the bioavailability of drugs absorbed in the stomach or upper intestine. This review examines physiological factors influencing gastric retention, including gastric emptying, pH variations, and absorption windows. Various GRDDS approaches—such as floating, swelling/expandable, mucoadhesive, high-density, magnetic, and raft-forming systems—are analyzed with respect to their mechanisms, formulation strategies, and evaluation parameters. Both natural and synthetic polymers play a crucial role in designing these systems, while innovations like 3D printing, smart polymers, and nanotechnology expand their potential. Despite advancements, challenges persist in translating laboratory success to clinical outcomes. GRDDS represent an innovation for improving oral bioavailability, enabling site-specific targeting, and enhancing therapeutic efficacy for drugs with narrow absorption windows or localized gastric action.

Keywords: *Gastroretentive drug delivery systems, bioavailability, mucoadhesive, therapeutic efficacy*

1. INTRODUCTION

1.1 Background on oral drug delivery

Oral drug delivery is a preferred method due to its convenience and patient compliance, but it faces several challenges that impact drug efficacy and bioavailability. These challenges arise from the complex environment of the gastrointestinal tract (GIT) and the physicochemical properties of drugs. Researchers have been exploring various strategies to overcome these barriers and enhance oral drug delivery systems. The following sections outline the key challenges and strategies in oral drug delivery. The enteric epithelium presents a significant barrier due to efflux transporters, enzymatic degradation, and tight junctions, which hinder drug absorption, especially for hydrophilic and high molecular weight drugs (Azman et al., 2022). First-pass hepatic metabolism further reduces drug bioavailability by metabolizing drugs before they reach systemic circulation (Azman et al., 2022).

Poor solubility and permeability are major issues affecting drug bioavailability. These factors are influenced by the drug's dissolution rate and its behavior in the GIT, which is affected by pH, enzymes, and microbial colonization (Pandey et al., 2024). Stability and storage issues, particularly with solutions and suspensions, also pose challenges for oral drug formulations (Loke, Jayakrishnan, Razif, et al., 2024). Nanotechnology platforms, such as polymer-based and lipid-based nanocarriers, have been developed to enhance drug stability and absorption by protecting drugs from the harsh GIT environment (D. Wang et al., 2023) (Almansour et al., n.d.). Novel formulations like nanoparticles, microemulsions, and microfabricated devices improve drug targeting and bioavailability by offering controlled and targeted release (Almansour et al., n.d.). Strategies such as solid dispersion, absorption enhancers, and self-nano emulsifying formulations (SNEF) are employed to improve drug solubility and permeability (Loke, Jayakrishnan, Mod Razif, et al., 2024).

While significant advancements have been made in addressing the challenges of oral drug delivery, the complexity of the GIT environment continues to pose hurdles. Future research may focus on further refining these innovative strategies and exploring new technologies to enhance therapeutic efficacy and patient outcomes. The significance of site-specific drug absorption in the gastrointestinal (GI) tract is paramount for optimizing therapeutic outcomes. Variations in drug absorption across different GI regions can influence bioavailability and efficacy. Understanding these differences allows for tailored drug delivery systems that enhance treatment effectiveness while minimizing side effects. The following sections elaborate on key aspects of this topic. The GI transit rate significantly affects drug absorption, as it determines the residence time of drugs at absorption sites (Kimura & Higaki, 2002). The GI-Transit-Absorption Model (GITA Model) has been developed to predict absorption kinetics by considering both transit rates and site-specific absorbability (Kimura & Higaki, 2002). The colon is increasingly recognized as a critical site for drug delivery, particularly for localized treatments of diseases like ulcerative colitis and colon cancer. Colon-targeted drug delivery systems (CTDDS) can enhance the therapeutic effect while reducing systemic side effects, making them suitable for proteins and peptides (Zheng et al., 2024). The physicochemical properties of drugs, along with the anatomy and physiology of the GI tract, play crucial roles in systemic absorption (Devadasu et al., 2018). A comprehensive understanding of these factors is essential for formulating effective drug products that achieve desired therapeutic goals (Devadasu et al., 2018).

1.2 Challenges in oral drug absorption

In contrast, while site-specific drug absorption can enhance therapeutic efficacy, it may also introduce complexities in drug formulation and delivery, necessitating advanced technologies to ensure consistent performance across diverse patient populations. Gastroretentive systems are essential in enhancing the bioavailability and therapeutic efficacy of orally administered drugs. These systems are designed to prolong the gastric residence time (GRT) of drugs, which is particularly beneficial for medications that are poorly soluble in alkaline environments or unstable in the intestine. By maintaining a drug's presence in the stomach for extended periods, gastroretentive drug delivery systems (GRDDS) can improve absorption rates and reduce drug waste, ultimately leading to better patient outcomes. The following sections outline the key aspects of the need for these systems.

1.3 Importance of gastric retention

GRDDS significantly enhance the bioavailability of drugs that are absorbed primarily in the stomach and upper small intestine. Prolonged GRT allows for a controlled release of the drug, minimizing fluctuations in plasma concentration (Vrettos et al., 2021). Conventional oral dosage forms often experience rapid transit times, leading to incomplete drug absorption (Harshdeep Desai*, 2024). GRDDS are particularly advantageous for drugs that are sensitive to gastric pH or require sustained release for therapeutic effectiveness. The market for gastroretentive systems is projected to reach USD 19.7 billion by 2028, indicating a growing demand for these innovative drug delivery methods (Harshdeep Desai*, 2024). Various technologies, including floating, bioadhesive, and expandable systems, are being developed to optimize drug retention in the stomach (Waknis & Narang, 2023). While gastroretentive systems offer significant advantages, challenges remain in their development, including the need for thorough understanding of gastrointestinal physiology and the formulation of effective delivery systems. These factors must be addressed to fully realize the potential of GRDDS in clinical applications.

1.4 Objectives of the review

The primary aim of this review is to explore and critically evaluate the latest innovations in gastroretentive drug delivery systems (GRDDS) that are designed to improve gastric retention time and optimize the oral bioavailability of drugs. The focus is on understanding the underlying mechanisms, formulation strategies, and the clinical relevance of GRDDS in enhancing therapeutic efficacy, especially for drugs with narrow absorption windows, poor solubility at higher pH, or localized action in the stomach. Fundamentals of GRDDS: Understanding the physiological challenges of gastric retention and the rationale for developing gastroretentive systems. Classification of GRDDS: A detailed overview of various systems including floating, bioadhesive, expandable, high-density, and superporoushydrogels. Formulation Approaches and Materials: Discussion of polymers, excipients, and novel materials used in designing GRDDS with controlled release properties. Pharmacokinetic and Pharmacodynamic Considerations: Evaluation of how GRDDS influence drug absorption, therapeutic window, and systemic bioavailability. Applications and Case Studies: Review of clinically approved products and investigational formulations for drugs like metformin, ciprofloxacin, domperidone, and clopidogrel.

2. PHYSIOLOGICAL CONSIDERATIONS IN GASTRIC RETENTION

2.1 Anatomy and physiology of the gastrointestinal tract

The stomach is a complex organ that plays a crucial role in digestion, nutrient regulation, and appetite control. Anatomically, it is the most dilated part of the digestive tract, located between the esophagus and the duodenum, and is divided into several regions including the cardia, fundus, body, and pylorus. The stomach's blood supply is primarily from the celiac trunk, and it is situated in the epigastric, umbilical, and left hypochondrial regions of the abdomen. Physiologically, the stomach functions to mix food with gastric secretions, forming chyme, and regulates its passage into the small intestine.

This process is controlled by neural and hormonal signals, including the enteric nervous system and hormones like gastrin and cholecystokinin (Bazira, 2023)(Daniels & Allum, 2005). The stomach is a muscular organ with a capacity of 1000–1500 ml in adults. It has two openings (cardiac and pyloric) and is divided into anterior and posterior surfaces by the greater and lesser omentum (Daniels & Allum, 2005). Blood supply is derived from the celiac trunk, reflecting its embryonic foregut origin (Bazira, 2023). The stomach acts as a temporary food store and mixes food with acid, mucus, and pepsin to form chime Gastric motility is regulated by the enteric nervous system and hormones such as gastrin and cholecystokinin, which influence muscle contractions.

2.2 Gastric emptying patterns and factors affecting retention

Gastric emptying rate is influenced by a variety of physiological, pathological, and genetic factors. Understanding these influences is crucial for both clinical practice and research, as they can affect drug absorption and overall gastrointestinal health.

Meal Composition: The volume, viscosity, and nutrient components of a meal significantly impact gastric emptying rates. High-fat meals, for instance, tend to slow down the process (Macdonald, 1996).

Hormonal Regulation: Intestinal hormones, such as glucagon-like peptide-1 (GLP-1), can slow gastric emptying. Genetic variations in the GLP-1 receptor have been linked to differences in gastric emptying rates among individuals (Yau et al., 2018).

Pathological Factors

Surgical Impact: Conditions such as pancreatoduodenectomy can lead to delayed gastric emptying (DGE), influenced by factors like intra-abdominal infection and blood loss during surgery (Liu et al., 2023).

Chronic Diseases: Conditions like diabetes and trauma can also alter gastric motility, leading to either accelerated or delayed emptying (Huang & Wang, 2012).

pH variations and their role in drug solubility

pH variations significantly influence drug solubility and, consequently, the effectiveness of gastroretentive drug delivery systems (GRDDS). The physiological pH of the gastrointestinal (GI) tract varies, affecting the solubility of drugs, particularly those classified as BCS class II, which are weakly basic and exhibit low solubility at higher pH levels. This variability necessitates the development of GRDDS that can maintain drug presence in the stomach for extended periods, enhancing bioavailability and therapeutic efficacy.

Impact of pH on Drug Solubility

pH-Dependent Solubility: Drugs like carvedilol show high solubility at low pH (1.2-5.0) and significantly lower solubility at higher pH (6.5-7.8) (Hamed et al., 2016).

Dissolution Behavior: The dissolution rate of weakly basic drugs is markedly higher in acidic environments, which is crucial for their absorption in the upper GI tract (Hamed et al., 2016).

Key Aspects of Absorption Window in Gastroretention

Physiological Constraints: The stomach's motility and gastric retention time (GRT) significantly influence drug absorption. GRDDS must overcome these challenges to maintain drug presence in the upper GI tract (Awasthi & Kulkarni, 2016).

Technological Approaches: Various systems, such as floating drug delivery systems (FDDS), bioadhesive systems, and expandable systems, have been developed to prolong GRT and optimize drug release in the absorption window (Faizi et al., 2012) (Ibrahim et al., 2019).

Drug Formulation: Drugs with NAW require specific formulations that release the active ingredient in the stomach or upper intestine, ensuring maximum absorption before the drug passes beyond the absorption site (Ibrahim et al., 2019).

While GRDDS show promise in enhancing drug bioavailability, challenges remain in translating in vitro success to effective in vivo performance, highlighting the need for continued research and development in this area (Awasthi & Kulkarni, 2016).

Factors affecting gastric residence time

Gastric residence time (GRT) is influenced by a variety of physiological and formulation factors that can significantly affect drug delivery and absorption. Understanding these factors is crucial for optimizing drug formulations and improving therapeutic outcomes. The following sections outline the key aspects affecting GRT.

Physiological Factors

Gender: Studies indicate that males generally have a faster GRT compared to females, with mean times of 3.4 hours versus 4.6 hours, respectively.

Age: Elderly individuals tend to experience prolonged GRT, with averages of 4.5 hours compared to younger adults.

Posture: The position of the body can also impact GRT, with variations observed in different postural states.

Formulation Factors

Floating Drug Delivery Systems (FDDS): These systems can enhance GRT by remaining buoyant in the gastric environment, thus prolonging drug release.

Particle Size and Density: Research shows that particle density has a more significant effect on transit time than size, influencing how long particles remain in the stomach.

Viscosity of the Gastric Contents: The viscosity of the fluid can alter the GRT, as higher viscosity can slow down the movement of particles. While these factors are critical for enhancing GRT, it is also important to consider that individual variability in gastric emptying can lead to inconsistent drug absorption, complicating therapeutic efficacy.

3. CLASSIFICATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

3.1 Floating Drug Delivery Systems (FDDS)

Floating drug delivery systems (FDDS) represent a significant advancement in pharmaceutical technology, designed to enhance drug bioavailability and therapeutic efficacy by prolonging gastric retention time. These systems utilize buoyant materials or effervescent agents to remain afloat in gastric fluids, thereby facilitating sustained drug release and targeted delivery within the gastrointestinal tract. The following sections outline the key aspects of FDDS.FDDS operates on a flotation mechanism that allows dosage forms to remain in the stomach longer than conventional systems, improving drug absorption and reducing waste (Kumar et al., 2024). The design often includes bilayer floating tablets, which are particularly effective for treating local gastrointestinal conditions like peptic ulcers.

3.1.1 Effervescent systems

Effervescent gastroretentive drug delivery systems (GRDDS) are innovative formulations designed to enhance the retention of drugs in the stomach, thereby improving their bioavailability and therapeutic efficacy. These systems utilize effervescence-inducing agents to create gas bubbles that help the dosage form float on gastric fluids, prolonging its residence time. This approach is particularly beneficial for drugs with limited solubility in alkaline conditions or those requiring localized gastric action. The following sections detail the mechanisms, advantages, and challenges associated with effervescent GRDDS.

3.1.2 Non-effervescent systems

Non-effervescent gastroretentive drug delivery systems (GRDDS) are innovative formulations designed to enhance the gastric residence time of drugs, thereby improving their bioavailability and therapeutic efficacy. These systems are particularly advantageous for drugs with a narrow absorption window or those that are unstable in alkaline environments. The development of non-effervescent GRDDS involves various strategies, including the use of polymers and excipients that ensure sustained drug release while maintaining buoyancy in gastric fluids.

3.2 Swelling and Expanding Systems

Gastroretentive Drug Delivery Systems (GRDDS) utilize innovative mechanisms to enhance drug bioavailability by prolonging gastric residence time. Among these, swelling and expandable systems are particularly noteworthy for their ability to expand in the gastric environment, thereby preventing premature gastric emptying and facilitating sustained drug release. These systems are designed using biocompatible polymers and hydrophilic materials that swell upon contact with gastric fluids, ensuring effective drug delivery for medications with narrow absorption windows.

3.3 Mucoadhesive/Bioadhesive Systems

Mucoadhesive and bioadhesive gastroretentive drug delivery systems (MGRDDS) are innovative formulations designed to enhance drug absorption by prolonging the residence time of dosage forms in the gastrointestinal tract. These systems utilize bioadhesive polymers that adhere to the gastric mucosa, facilitating intimate contact with the absorption surface and improving therapeutic efficacy. The following sections outline the key aspects of MGRDDS.

Mechanism of Action

Bioadhesion: The process involves the adhesion of polymers to biological tissues, particularly mucosal layers, enhancing drug retention (Borade et al., 2022)

Gastroretention: MGRDDS are designed to remain in the stomach longer, allowing for sustained drug release in the absorption zone, which is crucial for drugs that are primarily absorbed in the upper gastrointestinal tract.

3.4 High-Density Systems

High-density systems are a significant category within gastroretentive drug delivery systems (GRDDS), designed to enhance the bioavailability of drugs by prolonging their gastric retention time. These systems utilize a high-density formulation that allows them to settle in the stomach, thereby facilitating a controlled release of the drug at the site of optimal absorption. The following sections elaborate on the mechanisms, advantages, and challenges associated with high-density systems.

3.5 Magnetic Retention Systems

Magnetic systems for gastroretentive drug delivery have emerged as a promising approach to enhance the bioavailability of drugs that require prolonged gastric retention. These systems utilize magnetic forces to maintain the dosage form in the stomach, thereby extending the drug's residence time and optimizing absorption in the upper gastrointestinal tract. The following sections outline the key aspects of magnetic systems in gastroretentive drug delivery.

3.6 Raft-forming Systems

Raft-forming systems represent a significant advancement in gastroretentive drug delivery, enhancing drug bioavailability and providing sustained release profiles. These systems utilize a combination of gelling agents and gas-generating components to form a buoyant raft that remains in the gastric environment, allowing for prolonged drug release. The following sections detail the mechanisms, advantages, and applications of raft-forming systems.

Composition: Raft-forming systems typically include gelling agents like Isabgol and gas-generating agents such as sodium bicarbonate, which create a floating gel upon contact with gastric acid (Borade et al., 2022).

Buoyancy: The raft's ability to float is crucial for maintaining contact with the gastric mucosa, thus enhancing drug absorption in the upper gastrointestinal tract (Shree et al., 2022).

4. POLYMERS AND MATERIALS USED IN GRDDS

Polymers play a central role in the design and performance of gastroretentive drug delivery systems (GRDDS). Their physicochemical characteristics directly influence drug release mechanisms, gastric retention, mucoadhesion, swelling behavior, and biocompatibility. Broadly, they can be categorized into natural polymers and synthetic polymers, each with unique advantages and limitations.

4.1 Natural Polymers

Natural polymers are widely preferred in GRDDS due to their biocompatibility, biodegradability, and low toxicity. They often provide mucoadhesion, swelling, and gel-forming properties, making them suitable for enhancing gastric retention.

Practical Implications: Natural polymers improve safety profiles and are acceptable for long-term use. However, they show batch-to-batch variability and may have weaker mechanical strength, which can affect reproducibility in large-scale formulations.

4.2 Synthetic Polymers

Synthetic polymers are engineered to provide predictable, reproducible properties such as pH sensitivity, film formation, and controlled degradation. They are widely used to optimize drug release kinetics and enhance formulation stability.

Practical Implications: Synthetic polymers allow for precise drug release profiles and high formulation stability. Their drawbacks include higher cost and potential regulatory hurdles for safety in long-term use.

Table 1. Comparative Overview of Natural vs. Synthetic Polymers

Category	Polymer Examples	Key Roles in GRDDS	Advantages	Limitations	References
Natural Polymers	Chitosan, Alginate, Guar Gum, Pectin, Xanthan Gum	Mucoadhesion, swelling, gel formation, density modification	Biocompatible, biodegradable, low toxicity	Batch-to-batch variability, weaker mechanical strength	(Martău et al., 2019)
Synthetic Polymers	HPMC, Carbopol, Eudragit, Ethylcellulose	Controlled release (diffusion, swelling, erosion), film formation, pH sensitivity	Reproducible properties, tunable release profiles, high stability	Higher cost, safety concerns with prolonged use	(Nyamweya, 2021), (Olechno & Winnicka, 2019)

4.3 Polymer Selection Criteria

The selection of polymers for GRDDS depends on:

Mucoadhesion: Ensures retention in the stomach (e.g., chitosan, Carbopol).

Swelling Capacity: Enhances gastric residence (e.g., HPMC, guar gum).

Viscosity & Gel-Forming Ability: Helps control drug release (e.g., alginate, pectin).

pH-Sensitivity: Enables site-specific release (e.g., Eudragit).

Mechanical Strength: Ensures stability of dosage form during gastric motility.

5. IN VITRO EVALUATION:

5.1 Floating lag time

Floating lag time refers to the delay before a floating system, such as a pharmaceutical tablet, begins to float in a liquid medium. This concept is particularly relevant in the development of floating drug delivery systems, which aim to enhance the bioavailability of drugs by prolonging their retention in the stomach. The floating lag time is a critical parameter in ensuring the effectiveness of such systems, as it determines how quickly the tablet can start floating and thus begin its intended function.

Pharmaceutical Applications

Floating lag time is crucial in the formulation of sustained release floating tablets, such as those developed for metformin hydrochloride. By optimizing the combination of polymers like HPMC K15 and HPMC K100, researchers have successfully reduced the floating lag time to 1 minute, enhancing the drug's bioavailability and effectiveness (Djebbar et al., 2020). The use of effervescent agents like NaHCO3 and citric acid in specific quantities can significantly impact the floating lag time, as demonstrated in the formulation of metformin tablets (Djebbar et al., 2020).

Technological and Engineering Contexts

In the context of dynamic systems, the concept of "floating-time" is used in time optimal control methods to minimize the time of motion for multi-body systems. This involves adjusting time increments to achieve the shortest possible motion time, which is conceptually similar to minimizing lag time in pharmaceutical applications (Zhi et al., 2021). Floating lag time can also be related to the delay mechanisms in computational systems, where floating interruptions are managed to optimize processing efficiency. While the primary focus of floating lag time is in pharmaceutical applications, the concept of minimizing delay is also relevant in other fields such as computational systems and dynamic control. These diverse applications highlight the importance of understanding and optimizing lag time across various domains.

5.2 Swelling index

The swelling index is a critical parameter in the formulation of floating drug delivery systems, influencing both buoyancy and drug release profiles. Various studies have demonstrated that the swelling index is directly related to the concentration of hydrophilic polymers used in the formulations. This relationship is essential for optimizing the performance of floating tablets.

Influence of Polymer Concentration

Increased concentrations of Hydroxypropyl Methylcellulose (HPMC) significantly enhance the swelling index, which in turn improves the buoyancy and floating lag time of the tablets (Liang et al., 2023). For instance, formulations with higher HPMC concentrations showed better-controlled drug release, with the swelling index correlating inversely with the rate of drug release (Moussa et al., 2019)

Drug Release Mechanisms

The swelling index affects the drug release mechanism, with higher swelling indices leading to sustained release profiles. For example, formulations with a strong swelling capacity can prevent premature disintegration and control drug release over extended periods (Chen et al., 2015) . The release kinetics often follow non-Fickian diffusion, indicating a combination of swelling and erosion processes (Viswanadha et al., 2024).

Practical Implications

Floating drug delivery systems, such as those developed for Glipizide, utilize the swelling index to enhance gastric residence time and improve bioavailability, particularly for drugs with narrow absorption windows (Tripathi et al., 2019). While the swelling index is crucial for optimizing floating drug delivery systems, it is also important to consider other factors such as the drug's physicochemical properties and the overall formulation strategy, which can also significantly impact drug release and therapeutic efficacy.

5.3 Mucoadhesion strength

Mucoadhesion strength is a critical factor in the efficacy of floating drug delivery systems (FDDS), as it enhances the retention of the dosage form in the gastrointestinal tract, thereby improving drug bioavailability. Various studies have demonstrated that the choice of mucoadhesive polymers significantly influences the mucoadhesion strength and overall performance of these systems.

Key Factors Influencing Mucoadhesion Strength

Polymer Selection: The use of polymers such as Hydroxypropyl Methylcellulose (HPMC) and Carbopol has been shown to enhance mucoadhesion. For instance, increasing the concentration of Carbopol in formulations leads to a proportional increase in bioadhesive strength (Pan et al., 2023).

Formulation Composition: Floating beads and tablets developed with sodium bicarbonate and mucoadhesive polymers exhibit high mucoadhesion rates, with formulations achieving up to 93% mucoadhesion efficiency (Amin et al., 2016).

Swelling Properties: The swelling index of the formulations, influenced by the type and concentration of polymers, also plays a role in mucoadhesion. Higher swelling indices correlate with improved mucoadhesive properties(Sahu et al., 2017) . In contrast, while enhancing mucoadhesion strength is beneficial for drug retention, excessive mucoadhesion may lead to difficulties in the release of the drug, potentially affecting the therapeutic outcomes. Balancing mucoadhesion with controlled drug release remains a challenge in the design of effective FDDS.

5.4 Drug release studies

Floating drug delivery systems (FDDS) are innovative formulations designed to enhance the gastric retention time of drugs, thereby improving their bioavailability and therapeutic efficacy. These systems utilize buoyant tablets or microparticles that remain afloat in the gastric environment, allowing for prolonged drug release. The studies reviewed demonstrate various approaches to optimize drug release profiles in FDDS.

5.5 Formulation Techniques

Polymer Combinations: Various polymers such as PVP K30, HPMC K15M, and xanthan gum are employed to create floating tablets. These polymers help in achieving desired buoyancy and controlled drug release (Blynskaya et al., 2022).

Direct Compression and Granulation: Techniques like direct compression and wet granulation are utilized to prepare the tablets, ensuring optimal physical properties and drug release characteristics (Blynskaya et al., 2022).

Drug Release Mechanisms

Kinetic Models: Drug release from floating systems often follows non-Fickian diffusion, indicating a combination of diffusion and erosion mechanisms. Studies show that formulations exhibit varying release rates, with some achieving over 90% release in 6 hours (Blynskaya et al., 2022).

Buoyancy and Floating Time: Enhanced formulations demonstrate significant floating times (up to 12 hours), which is crucial for maintaining drug levels in the stomach.

5.6 In vivo/in vitro correlation (IVIVC)

In vivo/in vitro correlation (IVIVC) for floating drug delivery systems (FDDS) is crucial for predicting the in vivo performance of these formulations based on in vitro dissolution data. The establishment of IVIVC allows for more efficient drug development and quality control, particularly for FDDS, which are designed to enhance bioavailability by prolonging gastric retention. The following sections outline key aspects of IVIVC in the context of FDDS.

Importance of IVIVC in FDDS

Predictive Modeling: IVIVC serves as a mathematical model to estimate in vivo drug behavior from in vitro dissolution profiles, facilitating the prediction of pharmacokinetic parameters such as Cmax and Tmax (Davanço et al., 2020) .

Regulatory Compliance: Establishing IVIVC can reduce the need for extensive human studies, thus streamlining the regulatory approval process for new pharmaceuticals (Davanço et al., 2020).

Methodologies for Establishing IVIVC

Advanced Dissolution Testing: Novel biorelevant dissolution apparatuses mimic physiological conditions, improving the accuracy of in vitro tests for FDDS.

Computational Tools: Integration of machine learning and automated systems enhances the analysis of dissolution profiles, allowing for real-time monitoring and optimization of drug formulations.

Case Studies and Applications

Floating Microspheres: Research on floating alginate microspheres demonstrated successful IVIVC, with optimized

formulations achieving significant drug release and retention in the stomach.

Artificial GI Systems: These systems replicate the gastrointestinal environment, improving the correlation between in vitro dissolution and in vivo absorption.

While IVIVC is a powerful tool for predicting drug behavior, it is essential to recognize that variability in individual patient responses and physiological conditions can complicate these correlations. Thus, ongoing research is necessary to refine IVIVC methodologies and enhance their predictive capabilities.

5.7 Imaging and radiographic techniques

Floating drug delivery systems (FDDS) utilize innovative imaging and radiographic techniques to enhance drug delivery efficacy and patient outcomes. These systems are designed to remain buoyant in the gastric environment, allowing for prolonged drug release and improved bioavailability, particularly for drugs absorbed in the upper gastrointestinal tract.

Imaging Techniques in FDDS

MRI and CT Scans: These imaging modalities are crucial for evaluating the positioning of floating systems within the gastrointestinal tract. MRI can model drug diffusion based on infusion levels, while CT scans provide detailed anatomical insights for optimal catheter placement in intrathecal systems (Dupoiron et al., 2020).

Fluoroscopy: This technique is the gold standard for catheter placement, ensuring accurate positioning of drug delivery devices (Dupoiron et al., 2020).

Evaluation of FDDS Performance

In Vitro and In Vivo Studies: Recent advancements in FDDS have included various in vitro techniques to assess buoyancy and drug release profiles, alongside in vivo studies to evaluate therapeutic effectiveness.

Dynamic Imaging: Techniques like TC99 scintigraphy allow visualization of drug diffusion and velocity, enhancing understanding of drug release dynamics (Dupoiron et al., 2020).

Therapeutic Advancements

Personalized Medicine: The development of multifunctional FDDS capable of carrying multiple drugs and stimuli-responsive elements has revolutionized treatment strategies, particularly for chronic conditions. While FDDS shows promise in enhancing drug delivery, challenges remain in ensuring consistent performance across diverse patient populations and physiological conditions. Further research is needed to optimize these systems for broader clinical applications.

6. RECENT INNOVATIONS AND EMERGING TECHNOLOGIES

6.1. 3D printing in GRDDS

Recent innovations in 3D printing technologies have significantly impacted the field of drug delivery systems (GRDDS), enhancing the customization and efficiency of pharmaceutical formulations. These advancements enable the production of personalized dosage forms tailored to specific patient needs, thereby improving therapeutic outcomes. The following sections outline key innovations and emerging technologies in this domain.

Advanced Printing Techniques: Technologies such as Ink-Jet printing, Electrohydrodynamic Printing, and Fused Deposition Modeling are revolutionizing drug delivery by allowing precise control over drug release profiles and dosage forms.

Microfluidic Applications: 3D printing is increasingly used to develop microfluidic devices, which facilitate drug delivery and diagnostics, showcasing the versatility of this technology.

Regulatory Advances: The approval of products like Spritam® and new FDA guidelines have paved the way for broader applications of 3D printing in pharmaceuticals, enhancing its credibility and acceptance (S. Wang et al., 2023).

6.2. Smart polymers and stimuli-responsive systems

Recent innovations in smart polymers and stimuli-responsive systems have significantly advanced their applications across various fields, particularly in medicine and materials science. These materials are designed to respond to a wide range of stimuli, including physical, chemical, and biological triggers, enabling them to perform specific functions such as drug delivery, self-healing, and sensing. The development of these systems is driven by the need for more efficient, targeted, and controlled applications, especially in the biomedical sector. Below are key aspects of recent innovations and emerging technologies in this field.

6.2.1. Multifunctional Nanocomposites

Recent advancements have focused on creating multifunctional and stimuli-sensitive nanocomposites for drug delivery, which can respond to various stimuli like pH, temperature, and light to release drugs in a controlled manner. These nanocomposites are designed to improve spatial, temporal, and dosage control, enhancing the efficacy and safety of

therapeutic interventions (Zhang et al., 2019).

6.2.2. In Situ Gelling Systems

Stimuli-responsive in situ gelling systems have revolutionized drug delivery by transitioning from a liquid to a gel state upon exposure to specific stimuli, such as temperature or pH changes. These systems offer benefits like sustained drug release, improved patient compliance, and reduced side effects, making them highly suitable for applications in tissue engineering and regenerative medicine.

6.2.3. Polymeric Nanoparticles

Polymeric nanoparticles have emerged as promising carriers for targeted drug delivery, offering high drug loading capacity and site-specific release without leakage during transit These systems are functionalized to respond to stimuli such as redox conditions, light, and magnetic fields, providing precise control over drug release patterns.

6.2.4. Novel Synthetic Routes and Architectures

Innovations in synthetic routes and the design of novel architectures have expanded the functionality of smart polymers, enabling applications in self-healing materials, sensors, and actuators. These materials are engineered to respond to a variety of stimuli, including electric and magnetic fields, enhancing their versatility across different scientific disciplines.

While the advancements in smart polymers and stimuli-responsive systems are promising, challenges remain in ensuring their biocompatibility and biodegradability, particularly for biomedical applications. The ongoing research aims to address these issues, paving the way for safer and more effective smart materials in the future.

6.3. Nanotechnology and GRDDS

Recent innovations in nanotechnology and gastroretentive drug delivery systems (GRDDS) have significantly advanced therapeutic applications, enhancing drug efficacy and minimizing side effects. The integration of nanomaterials in drug delivery has led to the development of sophisticated systems that can target specific sites within the body, improving treatment outcomes for various diseases. This overview will explore key advancements in nanotechnology, the role of nanoparticles in GRDDS, and the challenges faced in clinical applications.

6.3.1. Key Advancements in Nanotechnology

Nanoparticle Types: Various nanoparticles, including liposomes, polymeric nanoparticles, and metallic nanoparticles, are being utilized for drug delivery, each offering unique properties for optimized drug encapsulation and release.

Stimuli-Responsive Systems: Recent developments include systems that release drugs in response to specific stimuli (e.g., pH, temperature), allowing for targeted therapy.

Biodegradable Nanocarriers: Innovations in biodegradable polymers have enabled the design of nanocarriers that protect drugs from degradation and facilitate site-specific delivery.

6.3.2. Role of Nanoparticles in GRDDS

Targeted Delivery: Nanoparticles enhance the delivery of drugs to the gastrointestinal tract, improving therapeutic efficacy for conditions like inflammatory bowel disease and colorectal cancer.

Enhanced Bioavailability: The nanoscale size of these carriers allows for better absorption and bioavailability of drugs, which is crucial for effective treatment.

6.3.3. Challenges and Future Directions

Regulatory and Safety Concerns: The integration of nanotechnology in drug delivery faces challenges related to regulatory approval and safety assessments, which must be addressed for successful clinical translation.

Personalized Medicine: Future research is focusing on personalized nanomedicine, combining nanotechnology with other emerging technologies to tailor treatments to individual patient needs. While the advancements in nanotechnology and GRDDS present exciting opportunities for improving drug delivery systems, there remains a need for ongoing research to address regulatory hurdles and ensure the safe implementation of these technologies in clinical settings.

6.4 Combination systems (e.g., floating + mucoadhesive)

Recent innovations in combination systems, particularly floating and mucoadhesive drug delivery systems (FDDS), have significantly advanced the field of pharmaceutical technology. These systems enhance drug bioavailability and therapeutic efficacy by increasing gastric retention time and improving adhesion to mucosal surfaces. The integration of novel materials and technologies has led to more effective drug delivery solutions.

6.4.1. Innovations in Mucoadhesive Systems

Advanced Polymers: Recent developments include the use of mucin-mimic polymers that enhance adhesion and prevent

biofilm formation, improving drug delivery efficiency.

Nanotechnology: The incorporation of nanoparticles in mucoadhesive systems has resulted in controlled and sustained drug release, optimizing therapeutic outcomes.

6.4.2. Floating Drug Delivery Systems

Gastroretentive Mechanisms: Floating systems utilize low-density formulations that remain buoyant in the gastric environment, prolonging drug release and absorption.

Combination Approaches: The synergy of floating and mucoadhesive properties allows for enhanced residence time and localized drug action, particularly beneficial for drugs requiring prolonged gastric retention.

While these innovations present significant advantages, challenges remain in ensuring consistent performance and patient compliance, necessitating ongoing research and development in this dynamic field.

Table 2. Recent Innovations in GRDDS with Clinical/Experimental Examples

Technology	Example Drug/Formulation	Clinical Status	Key Benefit	Reference
3D Printing	*Spritam® (Levetiracetam)*	FDA approved (2015)	Rapid disintegration, patient-specific dosing	https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207958Orig1s000MedR.pdf
	3D-printed *Metformin floating tablets*	Preclinical/Trials	Personalized gastric retention	(Alqahtani et al., 2023)
Smart Polymers	*Chitosan nanoparticles for H. pylori antibiotics*	Phase II trials	Mucoadhesion + targeted delivery	(Spósito et al., 2024)
	In situ gelling *Metformin* system	Preclinical	Sustained gastric release	(Wiwattanapatapee et al., 2023)
Nanotechnology	*Emend® (Aprepitant nanocrystals)*	FDA approved	Improved solubility & bioavailability	(Sivanathan et al., 2024)
	Clarithromycin-loaded chitosan nanoparticles	Clinical trials	Gastric retention + anti-H. pylori	(Cong et al., 2019)
Combination Systems	*Domperidone floating-mucoadhesive tablets*	Clinical evaluation	Enhanced bioavailability	(Daihom et al., 2020)
	Amoxicillin–Clarithromycin–Omeprazole raft system	Preclinical	H. pylori eradication	(Gupta et al., 2023)

7. CHALLENGES AND FUTURE PROSPECTS

Implementation Barriers: Issues such as data privacy, regulatory hurdles, and equitable access to technologies hinder widespread adoption. Ethical Considerations: The integration of PM raises ethical questions regarding cost-effectiveness and the need for clear guidelines in clinical practice. While personalized medicine holds significant promise for improving healthcare delivery, it also faces challenges that must be addressed to realize its full potential. The balance between innovation and ethical considerations remains a critical aspect of its evolution.

8. CONCLUSION

Gastroretentive drug delivery systems (GRDDS) have shown significant potential in transforming oral drug delivery by

addressing the challenges associated with poor solubility, instability, and limited absorption of conventional formulations. By extending gastric residence time, GRDDS optimize drug absorption, maintain consistent plasma levels, and enhance therapeutic efficacy, particularly for drugs that require localized gastric action or are absorbed in the upper gastrointestinal tract. The development of various systems—such as floating, mucoadhesive, expandable, and raft-forming—demonstrates the versatility of this approach. Furthermore, the incorporation of advanced technologies, including 3D printing, smart polymers, nanotechnology, and multifunctional hybrid systems, underscores the growing innovation in this field. However, variability in gastric physiology, patient-specific responses, and formulation complexity continue to pose challenges to clinical translation. Future research should concentrate on patient-tailored designs, regulatory harmonization, and scalable manufacturing to ensure successful application. Overall, GRDDS offer an effective platform for improving bioavailability, reducing dosing frequency, and enhancing patient compliance, establishing them as a cornerstone in the future of oral drug delivery.

Author Contribution

PC – Data curation, Data analysis, Experimental work, Original Manuscript draft writing, and editing; **KKC -** Supervision, Manuscript writing and editing.

Conflict of Interest

Both the authors approved the submission of the manuscript and have no conflict of interest.

Ethic statement

There were no human/animal samples used in this study.

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Generative AI statement

The authors utilized generative AI tools for paraphrasing and language editing of the manuscript; however, all AI-generated content was thoroughly reviewed, critically evaluated, and appropriately modified before incorporation into the final version of the manuscript.

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