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A REVIEW ON GASTRORETENTIVE DRUG DELIVERY SYSTEMS (GRDDS)

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ABSTRACT

Gastroretentive Drug Delivery Systems (GRDDS) represent a pivotal pharmaceutical strategy aimed at prolonging the residence time of a dosage form within the stomach. This review synthesizes the comprehensive research landscape of GRDDS, focusing on the underlying rationale, diverse technological mechanisms, influential physiological factors, and emerging technologies. The necessity for GRDDS is rooted in overcoming biological limitations, specifically targeting drugs with a **narrow absorption window (NAW)** in the proximal small intestine and providing sustained local therapy for gastric diseases.[1,2] We detail the principle mechanisms—including buoyancy (floating systems), adhesion (mucoadhesive systems), and physical expansion (swelling systems)—elucidating the formulation science and polymer selection critical to each.[4,12] Furthermore, the impact of physiological variability, particularly the **Migrating Motor Complex (MMC)** and the fed/fasting state, on *in vivo* performance is critically assessed.[6] Finally, we explore the future trajectory of GRDDS, highlighting advances in **3D printing** and smart material design that promise to enhance clinical predictability and patient-centric delivery (90, 100). This review serves as an authoritative reference, integrating findings from over a hundred key publications (References 1–100) to guide future research and clinical translation in this dynamic field.

KEYWORDS: Gastroretentive Drug Delivery Systems (GRDDS) represent a pivotal pharmaceutical strategy aimed at prolonging the residence time of a dosage form within the stomach.

1. INTRODUCTION

1.1. The Critical Role of Oral Drug Delivery and its Biological Constraints

The oral route remains the most preferred and widely utilized method for drug administration due to its inherent convenience, cost-effectiveness, and high patient compliance.[2] However, the journey of an orally ingested dosage form through the gastrointestinal (GI) tract is fraught with physiological barriers that often compromise its systemic availability and therapeutic efficacy. Key limitations include enzymatic degradation, first-pass hepatic metabolism, and, most notably, the highly variable and finite **transit time** through the absorption regions.[3,18]

1.2. The Physiological Impetus for Gastroretention

Gastroretentive systems were conceptualized specifically to circumvent the constraints imposed by rapid and erratic gastric emptying.[5,15] Extended gastric residence time (GRT) is essential for several classes of drugs.

1. Narrow Absorption Window (NAW) Drugs: Many pharmacologically active compounds, such as certain antibiotics (e.g., Ciprofloxacin - 73) and anti-hypertensives, are optimally absorbed only in the stomach or the proximal sections of the small intestine (duodenum and jejunum).[23] If the dosage form clears the stomach too quickly, the drug may bypass its primary absorption site before complete release, leading to reduced bioavailability and efficacy.[1] GRDDS ensure continuous release at the site of absorption.[30]

2. Drugs with Low Solubility in High pH: Compounds whose solubility drastically decreases in the increasingly alkaline environment of the distal GI tract benefit from prolonged residence in the stomach's acidic milieu.[2]

3. Local Therapy in the Stomach: GRDDS are highly effective for treating diseases localized in the stomach or the upper GI tract, such as peptic ulcers or the eradication of *Helicobacter pylori* (*H. pylori*) infection. Localizing high concentrations of antimicrobial agents, like Amoxicillin or Metronidazole, minimizes systemic exposure and resistance while maximizing therapeutic concentration at the target site.[72, 48, 78]

4. Sustained Release and Compliance: For drugs with short biological half-lives, GRDDS facilitate sustained release, reducing fluctuations in plasma drug levels and minimizing the required dosing frequency, which significantly enhances patient compliance.[18, 11]

1.3. Gastric Motility: The Determining Factor for Transit

The retention of a dosage form is fundamentally governed by gastric motility, specifically the cyclic pattern known as the **Migrating Motor Complex (MMC)**.[9] The MMC is a distinct

pattern of contractile activity in the stomach and small intestine, crucial for clearing residual content and non-digestible solids from the GI tract.

- **Fasting State (MMC Active):** During the interdigestion state, the MMC cycles every 90 to 120 minutes. Phase III, the "housekeeper wave," consists of intense peristaltic contractions that rapidly sweep undigested solids, including conventional dosage forms, through the pylorus into the small intestine.[7] Any GRDDS must resist this clearance mechanism.[6]

- **Fed State (MMC Inhibited):** The ingestion of a meal, particularly one high in fats and calories, suppresses the MMC, replacing it with irregular, tonic contractions termed the digestive pattern.[6] This period of sustained, non-sweeping motility allows solids larger than the relaxed pylorus) to be retained for several hours, a phenomenon known as **size-dependent retention**.[16] GRDDS exploit this fed-state physiology.[46]

2. Mechanisms of Gastroretention

GRDDS are categorized based on their primary physical or chemical strategy to overcome the forces of gastric emptying.[4]

2.1. Density-Based Systems: Floating and Sinking

Density modification is arguably the most explored and commercially viable technique for prolonging GRT.[2]

2.1.1. Floating Drug Delivery Systems (FDDS)

FDDS, also known as buoyant systems, maintain a density **significantly lower than the gastric fluid**, allowing them to float on top of the stomach contents (3, 30). Floating keeps the dosage form localized near the cardia, the highest part of the stomach, where the contractions are generally less forceful than the antrum.[8]

- **Effervescent Floating Systems:** These systems generate gas, typically carbon dioxide within the matrix upon contact with gastric fluid. The gas becomes entrapped within the hydrocolloid layer, reducing the overall bulk density.[45] Common gas-generating agents include sodium bicarbonate in combination with an acidic component like citric or tartaric acid.[76] The kinetic rate of production and the strength of the polymer matrix (e.g., HPMC) are critical to achieving a short floating lag time and maintaining buoyancy over several hours.[55, 41]

- **Non-Effervescent Floating Systems:** Buoyancy is achieved by incorporating internal air pockets or low-density materials.[10,25]

Examples include.

- **Porous Structures:** Utilizing highly porous materials or incorporating polymers that swell to form an external gel barrier around an inner low-density core.[32,5]
- **Air-Filled Chambers/Microspheres:** Formulations utilizing hollow structures, such as hollow microballoons or capsules containing air-filled chambers, to intrinsically reduce density.[27, 19, 20]

2.1.2. High-Density (Sinking) Systems

In contrast, high-density systems are designed to sink rapidly and lodge in the lowest part of the stomach, the antrum, or pylorus, relying on gravity and settling within the rugae or folds of the stomach lining.[81] These systems require a density significantly higher than gastric fluid achieved by using heavy inert materials as excipients.[16] While conceptually simple, their retention is less predictable as they must remain trapped until they erode or disintegrate sufficiently for passage.[4]

2.2. Mucoadhesive and Bioadhesive Systems

Mucoadhesive systems employ specialized polymers to physically adhere to the gastric mucosal surface, effectively immobilizing the dosage form.[12]

- **Mechanism of Adhesion:** Adhesion involves establishing physicochemical interactions between the polymeric surface of the dosage form and the glycoprotein layer of the mucus lining.[37]

These interactions typically include.

- **Hydration:** Hydrophilic polymers swell and interpenetrate the mucus layer.
- **Hydrogen Bonding:** Key functional groups on the polymer (e.g., Polycarbophil, Chitosan) form strong hydrogen bonds with the sialic acid and sugar chains of mucin glycoproteins.[58,71] Chitosan, a cationic polymer, is particularly effective due to electrostatic attraction with the negatively charged mucus at gastric.[36]

- **Challenges:** The efficacy of mucoadhesive systems is constrained by the continuous turnover and erosion of the gastric mucus layer, requiring the adhesion force to be greater than the detachment force caused by motility and fluid flow over the required retention period.[13] Mucoadhesive tablets[22] and patches/films.[52] have been investigated.

2.3. Swelling, Expanding, and Unfolding Systems

These systems rely on a drastic increase in size after ingestion to a dimension larger than the pylorus, physically preventing passage.[14]

- **Hydrogel-Based Swelling Systems:** Formulations utilize highly swellable hydrophilic polymers that rapidly absorb water from the gastric fluid and increase their size.[5] The expansion must be sufficient and rapid to prevent premature emptying.[44,31]
- **Superporous Hydrogels (SPH):** An advanced variant, SPHs possess a highly porous internal structure, allowing them to swell extremely rapidly—within minutes—to a large size.[64,66,33,68] This rapid kinetics minimizes the risk of clearance before full expansion.[65]
- **Mechanical Expanding/Unfolding Systems:** These devices are typically encapsulated in a small, easily swallowable form and are designed to unfold or change shape into a large, non-digestible structure upon entering the stomach.[29] Their retention is purely size-dependent, relying on the fed state of the stomach.[14]

3. Critical Factors Influencing Gastric Residence Time (GRT)

The efficacy and predictability of any GRDDS are fundamentally linked to their interaction with the complex physiological environment of the stomach.[40] Achieving prolonged gastric retention requires navigating the dynamic forces of gastric motility, which are influenced by both the patient's physiological state and the dosage form's intrinsic physicochemical properties.[6]

3.1. Physiological Factors Governing GRT

The primary challenge in designing a successful GRDDS is overcoming the **gastric emptying** process, which is controlled by two main motility patterns.[16]

- **The Migrating Motor Complex (MMC):** In the fasting state, the MMC initiates strong, cyclical contractions across the stomach and intestine every 90 to 120 minutes.[9,46] This "housekeeping" activity sweeps undigested material, including dosage forms, rapidly through the pylorus.[7] If a GRDDS is released during the active sweep phase of the MMC, its GRT can be drastically shortened, negating the retention strategy.[15,47]
- **The Fed State Motility:** The presence of food, especially caloric content, inhibits the MMC and triggers the digestive motility pattern.[6] This pattern involves less forceful, more localized contractions, which significantly **prolongs GRT** for dosage forms large enough to resist passage.[16] The **nature of the meal** (e.g., high-fat content) is a key determinant in sustaining this delayed emptying.[47]

- **Other Biological Factors:** Age, gender (females often exhibit slower emptying), posture, and diseases like diabetes can all influence the baseline gastric emptying time.[46,18]

3.2. Formulation Factors Governing GRT

The design and composition of the dosage form dictate which retention mechanism will dominate and how effectively it counters the MMC.[40,6]

- **Density:** This is paramount for floating systems. A density less than 1.004 { g/cm}^3is necessary for buoyancy.[35,4] High-density systems rely on a density greater than 1.5 \ { g/cm}^3to sink effectively.[81]
- **Size and Shape:** Dosage forms with a diameter **greater than approx 7.5 { mm}** show a marked increase in GRT because the pylorus restricts the passage of larger objects.[16,38] Single-unit systems are highly susceptible to size-dependent clearance if they break down into particles smaller than the pyloric aperture.[100]
- **Polymer Selection:** The choice of polymer dictates performance. For floating systems, polymers must generate gas effectively or form a robust, gas-trapping matrix.[45] For mucoadhesive systems, the polymer must exhibit strong bonding affinity with mucin.[36,58] For swelling systems, the polymer's swelling kinetics must be faster than the MMC cycle to achieve retention before clearance.[66]
- **Single vs. Multi-unit Formulations:** Multi-unit systems (e.g., beads or pellets) offer **superior safety margins** against dosage form failure, provide a more predictable release profile, and allow for the co-administration of incompatible drugs, as the failure of a single unit does not compromise the entire dose.[54,99]

4. Evaluation and Characterization of GRDDS

Rigorous testing, both *in vitro* and *in vivo*, is necessary to translate a successful laboratory formulation into a reliable clinical product.[51]

4.1. In Vitro Testing Simulating Gastric Conditions

In vitro testing must accurately mimic the gastric environment pH 1.2 and the mechanical forces involved.[87]

- **Buoyancy Testing:** This involves submerging the formulation in simulated gastric fluid (SGF) to determine the **floating lag time** (time until the tablet floats) and the **total floating duration**.[45,91] For effervescent systems, the dissolution/gas evolution rate is monitored alongside buoyancy.[76]

- **Mucoadhesion Assessment:** Techniques involve measuring the **adhesion force** exerted by the dosage form on an artificial membrane or excised gastric tissue, often using tensiometers.[37,52] The work of adhesion is a key parameter.[13]
- **Swelling/Erosion Studies:** For expanding systems, precise measurement of dimensional change over time, often coupled with mass loss determination, is required to confirm the system reaches a sufficient retention size.[31,85]
- **Drug Release Kinetics:** Dissolution studies are performed in SGF to characterize the controlled release profile—whether zero-order, first-order, or diffusion-controlled.[41]

4.2. In Vivo Evaluation and Imaging

Clinical assessment confirms the success of *in vitro* predictions, providing the definitive measure of **Gastric Residence Time (GRT)**.[42]

- **Gamma Scintigraphy:** This remains the **gold standard** for human GRT determination.[79] A non-absorbable radioactive marker is incorporated into the GRDDS. Tracking the movement of this marker using external radiation detection allows researchers to accurately map the formulation's location over time, differentiating between gastric retention and small intestinal transit.[79]
- **Imaging Modalities:** Magnetic Resonance Imaging (MRI) and traditional X-ray techniques are also employed to visualize the position and integrity of larger, specifically designed GRDDS systems *in vivo*.[79]
- **Pharmacokinetic (PK) Correlation:** The ultimate metric of success is improved PK profile. Studies involve comparing the AUC (Area Under the Curve) and of the GRDDS formulation against a conventional immediate-release (IR) formulation to quantify the bioavailability enhancement (2). Establishing an **In Vitro–In Vivo Correlation (IVIVC)** is a crucial regulatory step.[91,60]

5. Advanced and Emerging GRDDS Technologies

The field is rapidly moving toward "smart" and patient-centric systems to overcome the inherent variability associated with older technologies.[1,100]

5.1. Precision Manufacturing: 3D Printing and In Situ Gelling

- **3D Printing (Additive Manufacturing):** This technology allows for unprecedented control over the geometric complexity, internal structure, and localized drug distribution within a single dosage form.[90] Complex lattice structures can be printed to optimize buoyancy or swelling while precisely tailoring the erosion profile.[90]

- **In Situ Gelling Systems:** These are typically liquid or semi-solid formulations that undergo a phase transition (gelling) upon reaching the stomach, forming a viscous, retained matrix.[50,69] This strategy avoids issues related to swallowing large solid objects[88] The gelling is often triggered by pH change or temperature shift.[39]

5.2. Stimuli-Responsive and Intelligent Systems

Intelligent GRDDS utilize inherent environmental signals for triggered drug release or enhanced retention.[34,39]

- **pH-Responsive Materials:** Polymers that exhibit different degrees of swelling or adhesiveness depending on the stomach (e.g., swell significantly only in the lower of the stomach) are being developed.[39,66]
- **Erosion-Modulated Release:** Novel systems are designed to maintain their retention-conferring size through controlled erosion for a defined period, ensuring the drug is released gradually until the device is small enough to pass safely.[85]

5.3. Micro- and Nano-Scale GRDDS

For localized gastric therapy, especially for sensitive molecules like peptides, the focus shifts to particle engineering.[43]

- **Nanoparticle/Microparticle Delivery:** Mucoadhesive polymers are used to coat these small particles, allowing them to adhere briefly to the gastric mucosa to deliver local therapy before passing through the system.[59,89] Biodegradable nanoparticles are also explored for controlled, long-term release profiles within the stomach.[28]
- **Multifunctional Systems:** The emphasis is shifting toward combining multiple retention mechanisms—such as mucoadhesion with simultaneous buoyancy.[17] —or integrating the GRDDS with solubility enhancement strategies to tackle both residence time and absorption simultaneously.[82,83]

6. Clinical and Regulatory Considerations

While the promise of GRDDS is substantial, successful translation from laboratory bench to patient bedside requires navigating complex safety, tolerability, and regulatory hurdles.[1]

6.1. Safety and Tolerability in Clinical Use

Patient safety is paramount, particularly concerning dosage forms designed for prolonged retention.[95] For large, expanding mechanical systems, a primary concern is the potential for **gastric obstruction** or device failure.[95] The design must ensure that the device remains

intact for the therapeutic period but disintegrates or shrinks safely afterward to pass through the pylorus without complication.[85]

- **Patient-Centric Design:** Design considerations now emphasize minimizing risks while focusing on the patient experience, including factors like palatability and ease of swallowing, especially for large unit-dose systems.[75]
- **Biodegradability:** Future systems, particularly those that are expanding or structural, increasingly incorporate biodegradable materials to guarantee safe clearance following drug release.[84,100]

6.2. Clinical Trials and Human Studies

Clinical efficacy is typically demonstrated through **Phase I/II trials** that employ imaging and pharmacokinetic analysis.[70]

- **In Vivo Tracking:** Gamma Scintigraphy is critical for non-invasively tracking the dosage form's location in humans, confirming the actual GRT, and correlating it with plasma drug concentration.[79,97] Case studies, particularly in challenging areas like *H. pylori* eradication, provide crucial clinical validation.[78]
- **Predictability:** The challenge lies in ensuring that the *in vitro* performance, even with sophisticated models.[87], accurately predicts *in vivo* retention across a diverse patient population.[60]

6.3. Regulatory and Intellectual Property Landscape

Regulatory pathways for GRDDS can be complex, often crossing the boundaries between drug products and medical devices.[86]

- **Regulatory Guidance:** Specific guidance is needed to standardize testing and approval for these novel hybrid systems.[86] The regulatory focus includes safety data on the retention components and reliable IVIVC.[60, 91]
- **Patent Trends:** The extensive research in this domain is reflected in a continuous stream of patents, particularly in the areas of buoyancy and mucoadhesion, shaping the competitive landscape.[77,94,57]

6.4. Special Populations

The physiological variability in gastric motility is pronounced in certain populations, necessitating specialized GRDDS designs.[96]

- **Pediatric and Geriatric Use:** GRDDS formulations must be designed considering reduced gastric acid secretion and altered gastric motility often seen in older adults, as well as the unique swallowing and palatability constraints in pediatric patients.[96]

7. Conclusion and Future Outlook

7.1. Conclusion: Achievements and Current Status

Gastroretentive Drug Delivery Systems have matured into a key platform, providing proven methods—chiefly buoyancy, mucoadhesion, and swelling—to overcome the pharmacokinetic limitations imposed by the human gastrointestinal tract.[1,2] From the early concepts of floating systems.[3,30] to the development of sophisticated mucoadhesive patches[52] and rapid-swelling superporous hydrogels[64], the field has delivered tangible solutions for drugs with narrow absorption windows and local therapeutic needs.[23,72] However, two significant challenges remain: minimizing inter- and intra-subject variability and ensuring the non-toxic, predictable clearance of the dosage form post-release.[1, 95]

7.2. Future Directions in GRDDS

The future of GRDDS is characterized by a move toward systems that are adaptive, highly controlled, and personalized.[100]

- **Personalized Medicine via 3D Printing:** Additive manufacturing (3D printing) is poised to revolutionize the field by enabling the on-demand creation of complex, high-resolution devices with optimized density and erosion characteristics tailored to individual patient needs or specific drug requirements.[90]
- **Next-Generation Materials:** Research will continue to focus on creating superior polymers for hydrogels and nanofibers that exhibit enhanced swelling kinetics and mucoadhesive strength under dynamic gastric conditions.[33, 98, 93]
- **Multifunctional Systems:** The emphasis is shifting toward combining multiple retention mechanisms—such as mucoadhesion with simultaneous buoyancy[17]—or integrating the GRDDS with solubility enhancement strategies to tackle both residence time and absorption simultaneously.[82, 83] The rapid pace of innovation continues to yield new floating systems.[61, 62, 63]
- **Oral Diagnostics and Sensing:** Beyond drug delivery, GRDDS concepts are being adapted for use as retained diagnostic or sensing devices, capable of monitoring gastric parameters *in situ*.[100]

The successful clinical adoption of GRDDS will increasingly rely on demonstrating reliable *in vivo* performance and establishing clear regulatory pathways, ensuring that these innovative systems translate their technological superiority into genuine patient benefit.[100]

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