WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 13, 502-516. Review Article ISSN 2277–7105

GASTRORETENTIVE DRUG DELIVERY SYSTEMS, A STRATEGIC APPROACH FOR ENHANCED GASTRIC RETENTION AND THERAPEUTIC EFFICACY

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Article Received on
13 May 2025,

Revised on 02 June 2025,
Accepted on 23 June 2025

DOI: 10.20959/wjpr202513-37416

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ABSTRACT

Gastroretentive drug delivery systems (GRDDS) are innovative oral drug delivery technologies designed to prolong the gastric residence time of drugs, thereby improving bioavailability, especially for drugs that are preferentially absorbed in the stomach or upper gastrointestinal tract. This review highlights the physiological considerations, mechanisms of gastroretention, various types of GRDDS including floating, bioadhesive, expandable, and high-density systems, as well as recent advances in formulation strategies. Factors influencing gastric retention and current challenges are also discussed. The integration of GRDDS in therapy has shown significant clinical promise in optimizing therapeutic outcomes.

KEYWORDS: Gastroretentive, drug delivery, floating system, mucoadhesion, gastric retention, controlled release.

1. INTRODUCTION

Oral drug delivery remains the most preferred and convenient route for administration. However, conventional oral dosage forms often face challenges such as short gastric residence time and variable bioavailability. Gastroretentive drug delivery systems (GRDDS) offer a strategic solution by ensuring prolonged gastric retention and controlled release of the drug at the absorption site.[1] This is particularly advantageous for drugs that are unstable in the intestinal or colonic environment or are absorbed primarily in the stomach or upper small intestine.[2]

Oral drug delivery remains the most preferred and convenient route of administration owing to its non-invasive nature, patient compliance, and cost-effectiveness.[3] However, a major challenge in conventional oral drug delivery lies in the inability to control the gastric residence time of dosage forms. Drugs with a narrow absorption window in the upper gastrointestinal tract (GIT), those degraded by intestinal pH or enzymes, or intended for local action in the stomach may exhibit poor bioavailability and reduced therapeutic efficacy when administered through conventional oral routes. To overcome these limitations, **Gastroretentive Drug Delivery Systems (GRDDS)** have emerged as a promising strategy.[4]

GRDDS are designed to prolong the residence time of dosage forms in the stomach, thereby enhancing drug absorption, improving bioavailability, and maximizing therapeutic outcomes. By retaining the drug in the gastric environment for extended periods, these systems allow for sustained and controlled drug release at the site of absorption or action.[5]

Several physiological and formulation-related factors influence gastric retention, including gastric motility, pH, feeding state, and the physical properties of the dosage form. To address these variables, a variety of gastroretentive approaches have been developed, such as **floating systems, mucoadhesive systems, high-density systems, expandable systems**, and **super-porous hydrogel systems**.[6] Each of these technologies operates on a different mechanism to maintain the dosage form within the stomach, whether by buoyancy, adhesion to the gastric mucosa, or mechanical enlargement to prevent passage through the pylorus.[7]

In addition to improving therapeutic efficacy, GRDDS can also reduce dosing frequency, minimize drug fluctuations in plasma, and improve patient adherence. These advantages are particularly significant for drugs like metformin, ciprofloxacin, levodopa, and amoxicillin, which benefit from prolonged gastric residence.[8]

This review aims to provide a comprehensive overview of gastroretentive drug delivery systems, focusing on the physiological considerations, technological approaches, formulation strategies, and current research trends in the development of effective GRDDS. Special attention is given to the design parameters that influence gastric retention, drug release kinetics, and the clinical relevance of such systems in enhancing pharmacological responses.[9]

2. RATIONALE FOR GASTRORETENTIVE SYSTEMS

The development of Gastroretentive Drug Delivery Systems (GRDDS) is grounded in the need to overcome limitations associated with conventional oral drug delivery, particularly for drugs that exhibit poor absorption beyond the upper part of the gastrointestinal tract. GRDDS are specifically designed to prolong the gastric residence time of dosage forms, ensuring that the drug remains in the stomach or proximal small intestine for a sufficient duration to achieve optimal therapeutic outcomes.[10]

Several categories of drugs significantly benefit from prolonged gastric retention, and the rationale for developing gastroretentive systems is based on the following pharmacokinetic and physicochemical considerations:[11]

1. Drugs with a Narrow Absorption Window

Certain drugs are absorbed only from a specific region of the gastrointestinal tract, typically the duodenum or the upper part of the small intestine. Once the drug passes this limited window, absorption decreases drastically, leading to reduced bioavailability and subtherapeutic plasma concentrations.[12]

- Examples: *Levodopa, Riboflavin, Furosemide, Gabapentin*
- Justification: GRDDS maintain the drug in its absorption window for a longer period, enhancing systemic absorption and therapeutic efficacy.

2. Drugs that are Locally Active in the Stomach

Some drugs are intended to exert their action directly on the gastric mucosa. Rapid gastric emptying of conventional dosage forms can result in reduced efficacy and the need for frequent dosing.[13]

- Examples: *Antacids, Misoprostol, Sucralfate, Bismuth salts*
- Justification: By prolonging gastric residence, GRDDS enhance local drug concentration, extend duration of action, and reduce dosing frequency.[14]

3. Drugs Poorly Soluble at Higher pH

The solubility of certain drugs decreases significantly at the higher pH of the small intestine. When such drugs are released beyond the stomach, their dissolution and absorption become suboptimal.[15]

- Examples: *Diazepam, Verapamil, Cinnarizine, Ketoconazole*
- Justification: GRDDS ensure the drug is released and dissolved in the acidic environment of the stomach, leading to improved solubility and bioavailability.[16]

4. Drugs Degraded in the Colon

Some drugs are susceptible to degradation by colonic enzymes or microbial flora. Their therapeutic efficacy may be compromised if they transit rapidly through the stomach and reach the colon prematurely.

- Examples: *Ranitidine*, *Metformin*, *5-Fluorouracil*
- Justification: Gastroretentive systems minimize drug exposure to the colonic environment by restricting drug release to the gastric region, preserving drug integrity and effectiveness.[17]

3. FACTORS INFLUENCING GASTRIC RETENTION

The effectiveness of gastroretentive drug delivery systems (GRDDS) is highly dependent on the ability of the dosage form to remain in the stomach for a prolonged period. Gastric retention time (GRT) is a complex physiological variable influenced by several factors, both intrinsic and extrinsic. A thorough understanding of these factors is essential in designing GRDDS with predictable performance and consistent therapeutic outcomes.[18]

Below are the key factors influencing gastric retention

1. Gastric Motility and Emptying Rate

Gastric motility involves coordinated contractions of the stomach muscles to move contents toward the pylorus. These movements vary between the **fasted** and **fed** states:[19]

- In the **fasted state**, the stomach undergoes cyclic motility patterns known as the **Migrating Myoelectric Complex (MMC)**, which has four phases over a 2–3-hour cycle. The strong peristaltic waves in Phase III act as a "housekeeper" that clears indigestible contents, including dosage forms.[20]
- In the **fed state**, the MMC is interrupted, and the stomach exhibits continuous contractions that delay emptying. Dosage forms administered with food often exhibit **prolonged gastric residence**, making this timing beneficial for GRDDS.[21]

2. Fed or Fasted State

The presence or absence of food significantly affects gastric retention:

- **Fed State:** Increased viscosity, volume, and caloric content of the meal slow gastric emptying. Fatty and protein-rich meals particularly enhance GRT.[22]
- **Fasted State:** Rapid clearance occurs due to the MMC, reducing the effectiveness of GRDDS. Therefore, timing the dosage with food can enhance system performance.[23]

3. Density and Size of the Dosage Form

- **Density:** Low-density (less than gastric fluid, ~1.004 g/cm³) formulations float on gastric contents (floating systems), while high-density (greater than 2.5 g/cm³) formulations sink and resist peristaltic movement.[24]
- **Size:** Dosage forms larger than 7.5 mm in diameter are more likely to be retained in the stomach due to delayed passage through the pyloric sphincter.[25]

4. Patient Posture and Physiological Conditions

- **Posture:** The supine position may enhance gastric retention compared to an upright position in certain individuals, although this effect varies.[26]
- **Age and Health Status:** Elderly patients and those with certain conditions (e.g., diabetes, gastroparesis) often have delayed gastric emptying, which can prolong GRT.
- **Gender:** Some studies suggest that females may exhibit slower gastric emptying than males, potentially due to hormonal differences.[27]

5. Co-administration with Other Drugs

Certain medications can alter gastric motility and pH, influencing the retention of gastroretentive formulations:

- **Prokinetic agents** (e.g., metoclopramide) accelerate gastric emptying and may reduce retention.
- **Anticholinergics** and **opioids** delay gastric emptying, potentially enhancing GRT.[28]
- **H2 blockers and proton pump inhibitors** increase gastric pH, which may affect buoyancy and drug solubility for certain GRDDS.[30]

4. MECHANISMS OF GASTRORETENTION

GRDDS are designed using one or more of the following retention strategies:

4.1 Floating Systems

These systems remain buoyant on gastric fluid, enabling prolonged retention.[31]

- **Effervescent Systems:** Generate gas (e.g., CO_2) to float
- **Non-effervescent Systems:** Use polymers like HPMC, xanthan gum

4.2 Mucoadhesive Systems

These adhere to the gastric mucosa via interactions with mucin using polymers like carbopol, chitosan.

4.3 Expandable Systems

Unfold or swell in the stomach to prevent passage through the pylorus.[32]

4.4 High-Density Systems

Settle at the bottom of the stomach due to their density (>1.5 g/cm³), resisting gastric emptying.[33]

5. POLYMERS USED IN GRDDS

Natural Polymers	Synthetic Polymers
Guar gum, Xanthan gum	HPMC, Carbopol, Eudragit
Chitosan, Pectin	Polyvinyl alcohol (PVA)

6. EVALUATION OF GRDDS

A comprehensive evaluation of gastroretentive drug delivery systems is essential to ensure their functionality, efficiency, and reproducibility in prolonging gastric residence and achieving controlled drug release. The performance of GRDDS is assessed through **in vitro**, **ex vivo**, and **in vivo** methods. Key parameters include buoyancy, swelling, mucoadhesive strength, drug release behavior, and gastric retention time.[34]

Below are the major evaluation methods used

1. In Vitro Buoyancy and Floating Lag Time

Objective: To assess the floating behavior of the dosage form in simulated gastric conditions.

- **Floating Lag Time (FLT):** Time taken by the dosage form to emerge on the surface of the medium after introduction.[35]
- **Total Floating Time (TFT):** The duration the dosage form remains buoyant.

Method: The dosage form is placed in 900 mL of 0.1N HCl (pH 1.2) at 37 ± 0.5°C in a USP Type II dissolution apparatus. FLT and TFT are recorded visually.

Significance: A short lag time and prolonged floating duration are critical for effective gastric retention in floating drug delivery systems.

2. Swelling Index (SI)

Objective: To determine the extent of swelling of the dosage form in gastric fluid, which influences retention and drug release.

Method: The dosage form is weighed (W_0) and placed in 0.1N HCl at 37°C. At predetermined time intervals, it is removed, blotted, and reweighed (Wt).

$$\textbf{Swelling Index (\%)} = [(Wt - W_0) / W_0] \times 100$$

Significance: Higher swelling capacity indicates better gastric retention in expandable or swelling-based systems.

3. Mucoadhesion Strength

Objective: To measure the adhesive strength of mucoadhesive systems to gastric mucosa, ensuring prolonged attachment and retention.[36]

Method: Modified physical balance or **texture analyzer** is used. A section of goat or pig stomach is fixed to a platform, and the dosage form is brought into contact under light pressure. The force required to detach it is recorded in grams or Newtons.

Significance: Strong mucoadhesion enhances gastric residence time, especially in mucoadhesive systems.

4. Drug Release Kinetics

Objective: To evaluate the rate and mechanism of drug release from the gastroretentive system.

Method: In vitro dissolution studies are conducted using a USP apparatus (typically Type II) in 0.1N HCl. Samples are withdrawn at specific intervals and analyzed by UV spectroscopy or HPLC.

Kinetic Models Used

- **Zero-order model:** Drug release is constant over time.
- **First-order model:** Release rate depends on the concentration.
- **Higuchi model:** Describes drug release as a square root of time-dependent process based on Fickian diffusion.
- **Korsmeyer–Peppas model:** Describes drug release from polymeric systems with exponent "n" indicating the mechanism (Fickian, anomalous, etc.)

Significance: Understanding drug release profiles helps in optimizing the formulation for sustained or controlled delivery.

5. In Vivo Evaluation (X-ray Imaging and Gamma Scintigraphy)

Objective: To directly observe the **gastric residence time** and **positioning** of the dosage form within the stomach.

Techniques

- **X-ray Imaging:** Dosage forms are radiolabeled with barium sulfate and administered to human volunteers or animals. Serial X-ray images are taken at various time points to monitor movement and retention.
- **Gamma Scintigraphy:** A radiolabel (commonly ^{99}mTc) is incorporated into the dosage form. A gamma camera captures real-time imaging of the transit through the GI tract.

Significance: These methods offer precise, non-invasive visualization and quantification of gastric retention in vivo.

7. Applications of GRDDS

Gastroretentive drug delivery systems (GRDDS) have demonstrated significant clinical and pharmaceutical advantages for drugs that benefit from prolonged gastric residence. These systems not only enhance bioavailability but also enable sustained drug release, targeted delivery, and improved patient outcomes. Below are notable examples illustrating the successful application of various GRDDS technologies:[37]

1. Floating Tablets of Ciprofloxacin – Enhanced Bioavailability

Ciprofloxacin, a broad-spectrum fluoroquinolone antibiotic, has a narrow absorption window in the upper gastrointestinal tract. Its absorption decreases significantly when it passes into the lower intestines. Conventional oral formulations result in suboptimal bioavailability and necessitate frequent dosing.

- **GRDDS Approach:** Formulation of floating tablets using polymers such as hydroxypropyl methylcellulose (HPMC) and effervescent agents (e.g., sodium bicarbonate).
- **Mechanism:** The tablets float on gastric fluid, enabling prolonged retention in the stomach.
- **Outcome:** Sustained drug release over 12–24 hours and improved absorption due to extended contact with the upper GIT.
- **Clinical Relevance:** Enhanced therapeutic levels, reduced dosing frequency, and improved compliance in treating urinary tract and respiratory infections.

2. Mucoadhesive Delivery of Metformin – Prolonged Glycemic Control

Metformin, the first-line oral hypoglycemic agent in type 2 diabetes, has limited bioavailability due to its absorption predominantly in the duodenum and upper jejunum. Its short half-life necessitates multiple daily doses to maintain plasma concentrations.

- **GRDDS Approach:** Development of **mucoadhesive tablets or microparticles** using bioadhesive polymers like carbopol, chitosan, or sodium alginate.
- **Mechanism:** The dosage form adheres to the gastric mucosa, resisting gastric emptying and releasing the drug at a controlled rate.
- **Outcome:** Prolonged gastric residence and sustained drug release over 8–12 hours.
- **Clinical Relevance:** Stable plasma glucose levels, reduced postprandial hyperglycemia, improved glycemic control, and minimized gastrointestinal side effects associated with conventional dosing.

3. Floating Capsules of Misoprostol – Local Gastric Action

Misoprostol, a prostaglandin E1 analog, is used to prevent NSAID-induced gastric ulcers and to manage gastric mucosal damage. For maximal therapeutic benefit, the drug must act locally in the stomach lining.

- **GRDDS Approach:** Floating capsules using swellable and low-density polymers to ensure buoyancy.
- **Mechanism:** The capsule remains buoyant in the stomach, slowly releasing the drug at the site of action.
- **Outcome:** Enhanced local drug concentration, extended mucosal exposure, and improved protective effects on gastric tissues.
- **Clinical Relevance:** Effective prevention of NSAID-induced ulceration with reduced systemic side effects and better patient tolerability.

8. Recent Advances

The field of gastroretentive drug delivery has evolved significantly in recent years, driven by innovations in material science, nanotechnology, and drug formulation techniques. These advances aim to overcome limitations of conventional GRDDS by enhancing precision, responsiveness, and patient-centric customization. Below are some of the most promising recent innovations in the design and application of gastroretentive systems:[39]

1. 3D Printing for Customizable GRDDS

3D printing (additive manufacturing) has revolutionized pharmaceutical technology by enabling the production of complex, personalized dosage forms with high precision.

- **Application in GRDDS:** Fabrication of floating tablets, expandable devices, and compartmentalized systems with tailored drug release profiles.
- **Advantages**
  - Customization of drug dose, geometry, and buoyancy.
  - Layer-by-layer printing allows integration of multiple drugs or release phases.
  - Potential for patient-specific therapy, especially in pediatrics and geriatrics.
- **Examples:** 3D-printed floating tablets of theophylline and multi-layer gastric-retentive platforms have shown promising results in preclinical models.

2. Multi-Unit Particulate Systems (MUPS) for Consistent Drug Delivery

MUPS consist of numerous discrete units (e.g., pellets, microspheres, beads) encapsulated in a single dosage form, offering more uniform drug distribution and predictable pharmacokinetics.

- **Application in GRDDS:** Floating MUPS coated with gas-generating agents or bioadhesive polymers ensure better gastric retention and drug release consistency.
- **Advantages**
  - Reduced inter- and intra-patient variability.
  - Minimized risk of dose dumping.
  - Lower chances of irritation and improved mucosal tolerance.
- **Examples:** MUPS formulations of clarithromycin and metronidazole have been developed for *Helicobacter pylori* treatment with sustained gastric retention and effective bacterial eradication.

3. Nanotechnology for Targeted Gastric Delivery

Nanocarriers such as **nanoparticles, liposomes, and nanoemulsions** have emerged as efficient tools for site-specific delivery within the gastric environment.

- **Application in GRDDS:** Encapsulation of drugs into nanoparticles improves stability in the acidic stomach environment and enhances penetration into gastric mucosa.
- **Advantages:**
  - Enhanced mucoadhesion and residence time.
  - Targeted delivery to infected or diseased gastric tissues.
  - Controlled release and improved bioavailability.

- **Examples:** Mucoadhesive chitosan nanoparticles of amoxicillin for targeted delivery against *H. pylori* infections and nanoformulations of curcumin for gastric cancer therapy.

4. Smart Polymers for Responsive Systems

Smart (stimuli-responsive) polymers change their physicochemical properties in response to environmental triggers such as pH, temperature, or ionic strength.

- **Application in GRDDS:** Development of **pH-sensitive or thermo-sensitive** hydrogels and films that respond to gastric conditions.
- **Advantages:**
  - Site-specific drug release activated by gastric pH.
  - Enhanced retention through swelling or adhesion in acidic conditions.
  - Reduced risk of premature drug release in the esophagus or intestines.
- **Examples:** pH-sensitive hydrogel matrices using poly (acrylic acid) or Eudragit® polymers for drugs like famotidine and ranitidine, which require localized gastric action.

9. Challenges and Limitations

Despite significant progress in the design and development of gastroretentive drug delivery systems, several **physiological, formulation-related, and patient-specific factors** can hinder their performance and consistency. Understanding these limitations is critical for optimizing dosage form design and ensuring safe, effective therapy.[40]

Below are the major challenges associated with GRDDS:

1. Variability in Gastric Emptying Time

Gastric emptying time can vary considerably between individuals and within the same individual under different conditions. It is influenced by factors such as food intake, meal composition, circadian rhythms, emotional stress, disease states, and medications.

- **Problem:** Unpredictable emptying may cause premature expulsion of the dosage form into the small intestine before drug release is complete.
- **Impact:** Loss of gastroretention, incomplete drug absorption, and therapeutic failure.
- **Example:** Rapid gastric transit in fasted individuals may lead to reduced bioavailability of drugs like riboflavin or ciprofloxacin.

2. Difficulty Maintaining Buoyancy in the Fasted State

Many GRDDS, particularly **floating systems**, rely on the presence of gastric contents for effective buoyancy and retention.

- **Problem:** In the fasted state, the migrating myoelectric complex (MMC) produces strong peristaltic waves every 90–120 minutes, leading to quick expulsion of non-digestible materials, including floating dosage forms.
- **Impact:** Shortened gastric retention time, reduced effectiveness of floating systems, and decreased drug bioavailability.
- **Solution (Partial):** Administering the dosage form with a light meal may prolong retention, but dietary control is not always feasible or consistent.

3. Risk of Dose Dumping

Dose dumping refers to the unintended, rapid release of the drug from a controlled-release dosage form, which may lead to toxic plasma concentrations.

- **Problem:** GRDDS systems can be sensitive to mechanical forces, gastric fluid composition, or formulation instability, especially in the stomach's acidic environment.
- **Impact:** Sudden drug release may cause adverse effects, toxicity, or treatment failure, particularly in narrow therapeutic index drugs.
- **Example:** Improper polymer selection or degradation of matrix systems may trigger dose dumping in floating or swelling-based formulations.

4. Patient-Specific Variations (e.g., Elderly or Diseased Stomach)

Patient physiology plays a vital role in the performance of GRDDS. Conditions such as **diabetes, gastroparesis, peptic ulcers, and age-related gastric dysfunction** significantly alter gastric motility and pH.

- **Problem:** These variations affect retention time, drug solubility, and absorption.
- **Impact:** Altered therapeutic response, reduced predictability of drug release profiles, and potential need for dose adjustment.
- **Examples**
  - **Elderly patients** often exhibit delayed gastric emptying, which may enhance or unpredictably prolong drug retention.
  - **Diabetic gastroparesis** may lead to erratic gastric contractions, affecting GRDDS performance.

10. CONCLUSION

Gastroretentive drug delivery systems represent a promising strategy to optimize oral drug therapy by enhancing drug bioavailability and patient compliance. Continued research into

polymer science, formulation engineering, and patient-centered design is critical for the successful translation of GRDDS from the lab to clinical practice.

Understanding the interplay of these factors is critical in designing effective GRDDS. Formulation scientists must consider not only the drug's characteristics but also the physiological and behavioural aspects of the target population. A well-designed gastroretentive system should optimize these factors to achieve sustained gastric retention and enhanced therapeutic efficacy.

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