INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Gastroprotective Drug Delivery Systems and Their Role in Advancing Cardiovascular Therapeutics

Priti Kumari*, Amit Kumar

Roorkee College of Pharmacy, Dist. Haridwar, Uttarakhand.

ARTICLE INFO

Published: 07 June 2025
Keywords:
Cardiovascular drugs, Antihypertensive, Gastroprotective, GRDDS, In-vivo gastric retention, absorption window
DOI:
10.5281/zenodo.15615932

ABSTRACT

Cardiovascular drugs face significant therapeutic limitations due to narrow absorption windows, short half-lives, and extensive first-pass metabolism, resulting in poor bioavailability and frequent dosing requirements. Gastroprotective drug delivery systems (GRDDS) offer a compelling solution by prolonging gastric residence time to optimize drug absorption in the upper gastrointestinal tract. This review gives overview of distinct gastroprotective mechanisms floating, mucoadhesive, swelling, high-density, raft-forming, magnetic, super porous hydrogel, and dual-mechanism systems and their successful application to cardiovascular therapeutics. Key cardiovascular drugs including propranolol, atenolol, diltiazem, losartan, metoprolol, captopril, verapamil, and clopidogrel have demonstrated enhanced bioavailability, sustained release profiles, and improved patient compliance when formulated as GRDDS. The review highlights formulation strategies and also describes key evaluation parameters for GRDDS including buoyancy lag time, total floating duration, swelling index, density measurements, mechanical strength, in vitro drug release studies, and in vivo gastric retention studies. While physiological variations in gastric emptying remain challenging, emerging dual-mechanism systems and smart polymer technologies promise more reliable gastric retention. GRDDS represents a transformative approach for cardiovascular drug delivery, addressing fundamental pharmacokinetic limitations while advancing toward personalized therapeutic solutions.

INTRODUCTION

Oral drug delivery remains the most favored route of administration due to its ease, safety, and patient compliance. Yet, it is not without limitations especially for drugs that has narrow therapeutic index. Such compounds are only effectively absorbed within a specific region of the gastrointestinal (GI) tract. Once they pass beyond this site, their absorption drops sharply, leading to

***Corresponding Author:** Priti Kumari
Address: *Roorkee College of Pharmacy, Dist. Haridwar, Uttarakhand.*
Email ✉: pritikumari61100@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

poor bioavailability. Additionally, first-pass metabolism in the liver can significantly reduce the active drug reaching systemic circulation. Other hurdles such as rapid gastric emptying, short residence time in the stomach, and the need for frequent dosing in drugs with short half-lives further complicate effective oral therapy. These challenges highlight the urgent need for advanced delivery systems that can enhance drug retention, absorption, and therapeutic efficacy. [1, 2] Conventional oral drug delivery systems often fall short when it comes to overcoming the complex environment of the gastrointestinal tract. They are particularly ineffective for drugs that are best absorbed in the upper GI region, as these systems lack the ability to resist rapid gastric emptying. As a result, the drug may pass into the lower intestines or colon before its release is complete, leading to suboptimal absorption. This premature transit limits the drug's contact time with its ideal absorption site, resulting in incomplete release and reduced therapeutic efficacy. The inability of conventional systems to maintain gastric retention remains a critical barrier to maximizing oral drug performance. [3] To address these challenges, gastroretentive drug delivery systems (GRDDS) have been developed to prolong a drug's residence time in the stomach. By remaining in the upper GI tract, these systems enhance the absorption and therapeutic performance of drugs that would otherwise be poorly absorbed. GRDDS are especially valuable in several scenarios: targeting *Helicobacter pylori* infections with antibiotics like amoxicillin [4]; improving the bioavailability of drugs primarily absorbed in the stomach or upper intestine [5]; enhancing the solubility of weakly basic drugs, which dissolve better in acidic environments; and protecting drugs that degrade in the colon. By enabling controlled and site-specific release, GRDDS offer a promising solution to many limitations of conventional oral formulations. [6] Gastroretentive systems represent an advanced strategy in oral drug delivery, designed to prolong gastric residence and enable site-specific release for both systemic and local effects. By remaining in the upper gastrointestinal tract, these systems offer controlled and sustained drug release, improving contact time with the absorptive surface and thereby enhancing bioavailability. [7] Additional benefits of this system include improved therapeutic efficacy, reduced drug loss, enhanced solubility for drugs unstable in higher pH environments, and targeted delivery for conditions affecting the stomach or duodenum. [8] This approach is especially beneficial in the context of cardiovascular therapy, where maintaining steady-state plasma concentrations and improving bioavailability are critical for therapeutic success. Several cardiovascular drugs need to be formed as gastroretentive formulation due to their pharmacokinetic and physicochemical limitations. Drugs like propranolol, diltiazem, and isosorbide mononitrate exhibit a narrow absorption window, primarily in the stomach and upper small intestine, beyond which their bioavailability significantly drops [9-11]. Others, such as captopril, have a short biological half-life, requiring frequent dosing that can be mitigated through sustained release from a GRDDS [12]. In addition, some cardiovascular agents are unstable in the alkaline pH of the intestine or have pH-dependent solubility conditions that can lead to incomplete absorption when conventional oral forms are used. Formulating these drugs into GRDDS allows prolonged gastric retention, leading to more consistent plasma levels, reduced dosing frequency, and improved therapeutic outcomes. This is particularly important for chronic cardiovascular conditions, where maintaining steady drug concentrations is critical to prevent fluctuations in blood pressure or heart rate. [13] Gastroretentive drug delivery technologies are generally classified based on the key mechanism

that enables prolonged gastric retention. These include high-density systems that sink in gastric fluid, expandable or unfolding systems that increase in size to prevent passage through the pylorus, and magnetic systems guided by external magnets. Low-density systems, on the other hand, remain buoyant either due to intrinsic porosity, gas generation, or the use of low-density excipients. Mucoadhesive systems work by adhering to the gastric mucosa, thereby resisting gastric emptying. Overall, the main strategies to extend gastric residence time involve adhesion to the stomach lining, swelling to a size that delays transit, or controlling the density of the formulation to float or sink in the stomach environment. [14] This review provides an overview of various gastroretentive technologies and presents specific case studies of cardiovascular drugs successfully formulated into gastroretentive systems. Critical evaluation parameters for GRDDS assessment are discussed, encompassing both in vitro and in vivo methodologies, while current challenges and limitations are addressed alongside future perspectives that promise more reliable and personalized cardiovascular therapeutics.

Drug Candidates For Gastroprotective Drug Delivery System

Many physiological conditions lead to the need for development gastroretentive systems such as a narrow upper gastrointestinal absorption window, a short drug half-life, drug instability in the gastrointestinal tract environment, local activity in the upper part of the gastrointestinal tract, or poor solubility at alkaline pH.

Gastroretentive systems can increase the therapeutic effectiveness of a drug through the removal and/or the reduction of more than one physiological constraint. For example, studies in dogs have shown long-term absorption and sustained blood levels of levodopa when it was delivery in a sustained profile from a gastroretentive system, in opposition to non-gastroretentive controlled release system and to an oral solution providing immediate release. [15] The results demonstrated that the gastroretentive system was able to circumvent limitations such as the short half-life and narrow absorption window that limit both drug release and complete drug absorption. Many cardiovascular drugs are well-suited for GRDDS due to their pharmacokinetic and physicochemical properties. These drugs often exhibit a narrow absorption window in the upper gastrointestinal tract, have short biological half-lives, or are unstable in the alkaline environment of the intestine. For instance, propranolol is highly lipophilic and undergoes significant first-pass metabolism, resulting in only about 25% reaching systemic circulation; its short half-life necessitates multiple daily doses, making it a candidate for GRDDS to enhance bioavailability and reduce dosing frequenc. [16] Similarly, captopril has a short half-life of 1–2 hours and is primarily absorbed in the duodenum; it becomes unstable at higher pH levels, limiting its absorption in the lower gastrointestinal tract. [17] By formulating these drugs into GRDDS, it is possible to prolong their gastric residence time, ensuring a more consistent absorption in the upper gastrointestinal tract, enhancing bioavailability, reducing dosing frequency, and improving patient compliance.

Types of GRDDS

Gastroretentive drug delivery systems come in various forms, each designed with unique mechanisms to keep medications in the stomach longer. Understanding these different approaches helps researchers choose the most suitable system for specific drugs and therapeutic needs.

1.1 Floating Systems

Floating drug delivery systems are formulated to have a lower density than gastric fluids, enabling them to remain buoyant in the stomach. They can be classified into effervescent systems—using gas-generating agents like sodium bicarbonate—and non-effervescent systems that rely on swellable polymers such as hydroxypropyl methylcellulose (HPMC). These systems help prolong gastric residence and improve drug bioavailability. [8, 18]

1.2 Mucoadhesive Systems

Mucoadhesive systems utilize polymers capable of adhering to the gastric mucosa, thereby increasing the retention time of the dosage form. Polymers like carbopol, chitosan, and polycarbophil facilitate adhesion via electrostatic or hydrogen bonding interactions. [19]

1.3 Swelling and Expandable Systems

These systems expand or swell upon exposure to gastric fluids, achieving a size large enough to resist gastric emptying. Commonly used swellable polymers include HPMC and polyethylene oxide. They are effective in sustaining drug release over extended periods. [20, 21]

1.4 High-Density Systems

These systems are formulated with high-density excipients to achieve a dosage form density exceeding 2.5 g/cm³, causing them to settle at the gastric antrum. The elevated density provides resistance against peristaltic contractions, thereby prolonging gastric residence time through gravitational retention in the lower gastric region. [22]

1.5 Raft-Forming Systems

These systems form a cohesive, floating raft on the gastric fluid's surface upon contact with it. Typically used for gastroesophageal reflux treatment, they contain gel-forming agents like sodium alginate and effervescent compounds. [23]

1.6 Magnetic Systems

Magnetic GRDDS incorporates internal magnets in the formulation and require an external magnet to localize and retain the dosage form in the stomach. While promising in theory, they require patient compliance and precise control. [24]

1.7 Superporous Hydrogels

These systems swell rapidly due to their high porosity and large surface area. Composed of hydrophilic polymers, they can expand within minutes to a large size, promoting gastric retention. [25]

1.8 Dual or Multi-Mechanism Systems

To overcome the limitations of individual systems, formulations combining two or more retention strategies like floating and mucoadhesion are developed. These multi-mechanism systems aim for improved stability and prolonged gastric retention. [18]

Table 1: Summary of Gastroprotective Drug Delivery Systems (GRDDS)

Type of GRDDS	Formulation Design	Advantages	Disadvantages	Examples	References
Floating Systems	Low-density systems that float over gastric fluid using gas-generating agents	Prolongs gastric residence time; increases	Requires sufficient gastric fluid; not suitable for drugs that	Floating tablets of ciprofloxacin, HBS (Hydrodynamicall	[18, 26]

	(e.g., $NaHCO_3$) or swellable polymers	bioavailability of drugs with narrow absorption window	irritate the stomach	y Balanced Systems)	
Effervescent Floating Systems	Uses effervescent agents like sodium bicarbonate and citric acid in a matrix	Rapid floatation and good in vivo retention	Dependent on food and gastric motility	Effervescent metronidazole tablets	[27]
Non-effervescent Floating Systems	Swellable or gel-forming polymers like HPMC, xanthan gum	Longer floatation time, suitable for sustained release	Risk of dose dumping; lag in floatation	HPMC based Mebeverine HCl and Hydralazine HCl matrix tablet	[28, 29]
Mucoadhesive Systems	Use of bioadhesive polymers (e.g., carbopol, chitosan) that adhere to gastric mucosa	Site-specific drug delivery; extended gastric retention	Mucosal turnover can reduce adhesion time	Mucoadhesive tablets of amoxicillin, Chitosan based mucoadhesive tablet of ibuprofen	[30, 31]
Swelling Systems	Polymers that swell in gastric fluid to a size > pyloric sphincter	Prevents premature passage; good for controlled release	Risk of gastric obstruction if not properly designed	Swellable matrices of propranolol HCl, Ciprofloxacin HCl	[32, 33]
High-Density Systems	Density > 2.5 g/cm^3 to sink and remain in the stomach	Effective for drugs requiring lower GI tract exposure	Technically challenging; limited polymer options	Barium sulfate based tablets	[34]
Raft-forming Systems	Forms a viscous, cohesive gel raft that floats on gastric contents	Mainly used for local effect in the stomach (e.g., antacids)	Not suitable for systemic delivery	Alginic acid–based Gaviscon®	[35]
Magnetic Systems	Formulation contains internal magnets; external magnet controls positioning	Targeted gastric retention	Requires patient compliance and an external magnet device	Ferrite powder based magnetic GRDDS	[36]
Expandable Systems	Unfold or swell to a large configuration that resists gastric emptying	High potential for controlled release	Risk of GI obstruction; complex design	multi-component gastroretentive expandable drug delivery system of Metformin	[37]
Superporous Hydrogels	Rapid swelling hydrogels with superporous structure	Quick expansion; good	Sensitive to pH and ionic strength	Superporous hydrogel tablet dosage forms of esomeprazole,	[25, 38]

		mechanical strength		Superporous hydrogel beads of ranitidine	

Gastroprotective Drug Delivery Systems For Cardiovascular Drugs

Cardiovascular drugs often present formulation challenges due to poor bioavailability, short half-life, or narrow absorption windows limited to the upper gastrointestinal tract. GRDDS have been explored as a solution to enhance bioavailability, prolong therapeutic effect, and improve patient adherence (Figure 1). This section highlights real-world examples of GRDDS designed for cardiovascular drugs, focusing on formulation strategies and their resulting improvements.

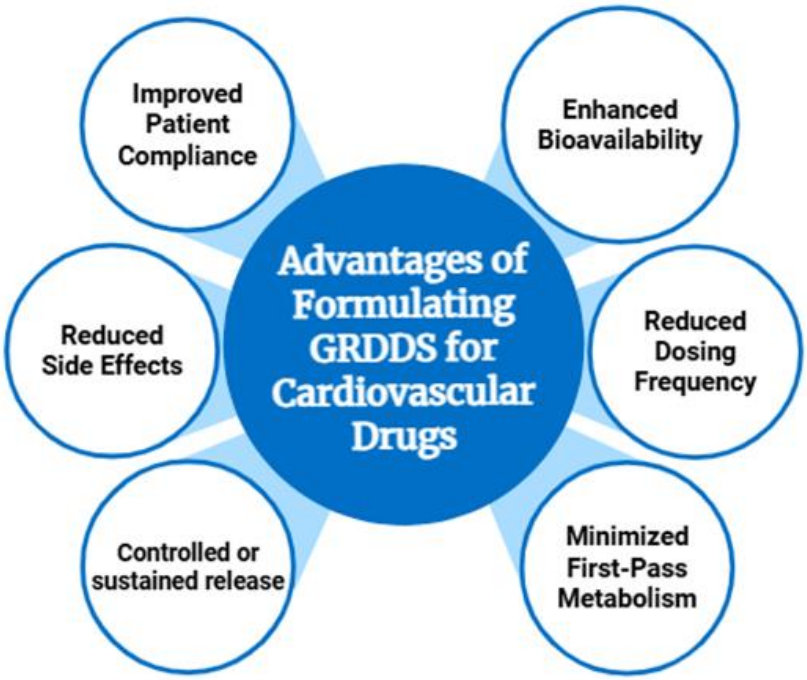

Figure 1: Advantages of GRDDS in Cardiovascular Therapy

Propranolol's short half-life, high first-pass metabolism, and the fact that food increases its bioavailability make it suitable for gastroretentive systems. As an acid-soluble basic drug where P-glycoprotein influences absorption, it benefits from prolonged gastric residence. Jagdale et. al., developed floating tablets by blending propranolol hydrochloride with HPMC, HPC, sodium bicarbonate as a gas-generating agent, and diluents, followed by direct compression. The matrix tablets swelled upon contact with aqueous medium. Formulations with xanthan gum demonstrated good drug-retaining abilities but poor floating capabilities. Formulation containing HPMC K4M provided optimal results with 92% drug release over 18 hours, and X-ray evaluation confirmed 4-hour gastric retention. [16] Atenolol is a beta-1 selective adrenergic blocker with limited oral bioavailability due to poor absorption in the lower gastrointestinal tract. Rao et. al., formulated a gastroretentive floating tablet of atenolol using hydroxypropyl methylcellulose (HPMC K4M), guar gum, and sodium bicarbonate. The formulation was prepared by direct compression,

with HPMC providing the gel matrix, guar gum slowing the release through its viscosity, and sodium bicarbonate generating gas for buoyancy. The optimized tablets showed a sustained drug release profile, delivering approximately 99% of atenolol over 24 hours while maintaining prolonged gastric retention. The drug release followed a non-Fickian diffusion mechanism, indicating a balance of diffusion and polymer relaxation. [39] Building on similar principles in a different study by Gunda et. al., developed atenolol floating tablets with varying amounts of HPMC K15M and sodium bicarbonate using 3^2 factorial design. The optimized formulation showed optimal performance, achieving controlled drug release (~99% over 24 hours), good buoyancy, and close similarity to a marketed product. Drug release followed Higuchi kinetics with a non-Fickian (Super Case-II) mechanism, suggesting diffusion through a swollen matrix combined with polymer relaxation. Results confirmed that increasing polymer concentration slowed drug release, while higher sodium bicarbonate levels enhanced it. [40] Combination therapy atenolol and simvastatin was formulated in the form of gastroretentive bilayer floating tablets; simvastatin was formulated as an immediate-release layer, and atenolol as a sustained-release layer. Tablets were prepared by direct compression using HPMC K100 (37.5%) as the release-retarding polymer and sodium bicarbonate as the gas-generating agent. The immediate-release layer contained sodium starch glycolate to ensure rapid disintegration. The optimized formulation floated for over 12 hours with a lag time of about 9 minutes, released over 96% of simvastatin within 15 minutes, and sustained atenolol release over 12 hours by diffusion. These results demonstrate a successful biphasic release profile suitable for combined therapy in hypertension and dyslipidemia. [41]

Diltiazem Hydrochloride is a calcium channel blocker used to treat hypertension and angina. It undergoes extensive first-pass metabolism via cytochrome P-450 CYP3A, resulting in low oral bioavailability (30–40%). With a half-life of 3.5 hours, frequent dosing and absorption limited to the upper intestine, it is a suitable candidate for gastroretentive delivery. Chandira et. al., developed floating tablets using an effervescent approach and direct compression method. Hydrophilic polymers (HPMC K4M, HPMC K15M), a hydrophobic polymer (ethylcellulose), and excipients like sodium bicarbonate, citric acid, magnesium stearate, talc, and lactose were used in various ratios. The optimal formulation showed a lag time of only a few seconds and floated for over 12 hours releasing 99.81% drug release over that duration. [42] Similarly, in in another study, Kalidindi et al. developed sustained-release microspheres of diltiazem hydrochloride using ionotropic gelation, incorporating sodium alginate, HPMC K15M, and carbopol 934 in various combinations. The optimized formulation demonstrated a mean particle size between 6.1 and 9.2 μm, high entrapment efficiency ranging from 70% to 94.6%, and a controlled drug release of up to 96%. Among the tested polymers, carbopol 934 proved most effective in controlling drug release kinetics in the final sustained-release microsphere formulation. [43] Losartan potassium (LP), an angiotensin receptor blocker for hypertension, has poor solubility at higher pH, which limits its bioavailability. To address this, an effervescent floating matrix tablet (EFMT) was developed by Rahamathulla et. al., using direct compression with HPMC-90SH 15,000, karaya gum, and sodium bicarbonate. The goal was to prolong gastric residence time and enhance drug absorption in the stomach. The tablets underwent evaluation for pre- and post-compression properties, in vitro buoyancy, swelling, and drug release. All formulations showed acceptable

physical characteristics, floated within 1 minute, and remained buoyant for over 24 hours. The optimized formulation demonstrated non-Fickian diffusion with complete drug release over 24 hours and excellent floating behavior in vivo, as confirmed by X-ray imaging in rabbits. Pharmacokinetic studies indicated improved bioavailability of the EFMT compared to the oral solution [44]. Losartan potassium has also been formulated into a non-effervescent floating tablet to enhance gastric residence time and prolong drug release. Chitosan and karaya gum were used as matrix-forming agents, while Accurel® MP 1000 served as the floating aid. Tablets were prepared by direct compression and evaluated using FTIR and DSC, confirming drug–polymer compatibility. Pre-compression parameters met pharmacopoeial standards. The tablets exhibited immediate buoyancy with no lag time and floated for over 12 hours. In vitro studies showed sustained drug release through swelling and gelation mechanisms. In vivo X-ray imaging confirmed gastric retention for 12 hours, and accelerated stability testing demonstrated tablet stability for over six months. These results suggest that the non-effervescent floating tablet of losartan potassium is a promising once-daily formulation for effective hypertension management [45]. In another study by Patel et al. a gastroretentive raft-forming tablet of losartan potassium was formulated using direct compression, with polymers such as HPMC K4M, xanthan gum, and carbopol 971P at varying concentrations. Sodium bicarbonate and sodium alginate were included as gas-generating and foaming agents to support buoyancy. The optimized formulation exhibited a floating lag time of 20 minutes, remained buoyant for up to 12 hours, and excellent in vitro drug release (98.88% over 12 hours), demonstrating effective sustained-release behavior. [46] Varshi et. al., developed a gastroretentive floating tablet of metoprolol succinate to enhance gastric retention and improve drug bioavailability. Metoprolol succinate, a β1-selective blocker used for hypertension, arrhythmia, and angina, has only 48% oral bioavailability due to limited absorption in the lower gastrointestinal tract. Floating tablets were formulated using hydrophilic polymers (HPMC K4M, K15M, K100M, and PEO 303) and sodium bicarbonate as a gas-generating agent to reduce lag time and sustain drug release. Results confirmed that the formulations exhibited good floating ability with a floating lag time of 20 s, total lag time of up to 12 h and prolonged release of 100 % in 12h and meeting all the quality standards. This indicates that floating tablets of metoprolol succinate offer a promising alternative to conventional dosage forms for improved therapeutic efficacy. [47] Porous floating tablets of captopril were developed by Reza et. al. using zein as the matrix-forming polymer and l-menthol as a porogen. The tablets were manufactured via direct compression, and sublimation of l-menthol created internal pores that lowered tablet density, enabling immediate and prolonged buoyancy in gastric fluid for over 24 hours. Drug release was influenced by the degree of porosity—higher porosity led to faster release rates, which could be controlled by adjusting l-menthol levels. The tablets also demonstrated strong mechanical integrity under wet conditions, indicating their ability to endure the gastric environment. In vivo studies in New Zealand rabbits confirmed extended gastric retention and sustained drug release, with a longer Tmax and mean residence time compared to immediate-release tablets. These results support the use of zein-based porous systems as a promising approach for enhancing gastric retention and therapeutic performance of captopril. [48] Verapamil, a calcium channel blocker used in cardiovascular therapy, has a short half-life that necessitates frequent dosing. Kumar et al. developed microcapsule-based formulations of verapamil using ethylcellulose (EC) and cellulose

acetate (CA) via a hot melt technique, varying the drug-to-polymer ratios. These microcapsules were later compressed into matrix tablets to compare release profiles. In vitro studies in 0.1 N HCl showed that drug release duration increased with higher polymer content, with the 1:1 drug-to-polymer ratio providing the most prolonged release. Specifically, EC-based and CA-based formulations extended drug release up to 7 and 6 hours, respectively, while matrix tablets prepared from these microcapsules achieved controlled release for up to 12 hours. The optimized formulations followed Higuchi kinetics and offered a promising approach for sustained once-daily oral delivery of verapamil. [49] Rao et. al., developed a floating drug delivery system for clopidogrel bisulphate aimed at enhancing its bioavailability while minimizing side effects such as gastric bleeding and the risk of drug resistance. Floating tablets were formulated using the direct compression method with varying concentrations (20%, 25%, and 30% w/w) of xanthan gum, HPMC K15M, and HPMC K4M. Sodium bicarbonate (15% w/w) was used as a gas-generating agent, and microcrystalline cellulose (30% w/w) served as a filler. The formulations were evaluated for their buoyancy and the impact of polymer type and concentration on the drug release profile. In vitro dissolution studies in 0.1 N HCl indicated that all batches followed first-order and Higuchi release kinetics, with non-Fickian diffusion as the primary mechanism. Drug release was significantly influenced by polymer concentration, with higher levels slowing the release ($P < 0.05$). The optimized formulation containing 25% xanthan gum showed optimal floating behavior (floating lag time of less than 1 minute and total floating time of more than 16 hours) and controlled drug release, making it the most promising candidate. [50]

Evaluation Parameters for Gastroprotective Drug Delivery Systems

Evaluation of gastroprotective drug delivery systems (GRDDS) involves specialized tests that directly assess their ability to remain in the stomach and release the drug effectively. Important parameters include buoyancy lag time, which measures how quickly the dosage form begins to float in gastric fluid, and total floating duration, indicating how long it stays buoyant to ensure prolonged gastric retention. The swelling index and water uptake tests evaluate how much the formulation expands upon contact with gastric fluid, contributing to its retention. Measuring the density or specific gravity confirms whether the system is sufficiently light to float. Physical strength tests like hardness and friability ensure the dosage form can withstand handling and gastric motility. In vitro drug release studies track how the drug is released over time, ensuring controlled and sustained delivery. For mucoadhesive systems, bioadhesive strength testing assesses the formulation's ability to stick to the gastric mucosa. Lastly, in vivo gastric retention studies, often using imaging techniques, verify how long the system remains in the stomach in a living organism. The tests are described along with ideal limits in the following section:

Buoyancy Lag Time and Total Floating Duration

For floating GRDDS, buoyancy is a critical parameter. The buoyancy lag time (BLT) represents the delay before the dosage form begins to float upon immersion in gastric media (typically 0.1 N HCl, pH 1.2). Floating time is determined by using the USP disintegration apparatus containing 900mL of 0.1 N HCl solution as a testing medium maintained at 37 ± 0.5ºC. The time required to float different dosage forms is noted as floating (or buoyancy) lag time and floating duration of the

dosage form is determined by visual observation. [51] An ideal system should exhibit a BLT of less than 2 minutes. The total floating duration reflects how long the dosage form remains buoyant, with successful systems maintaining flotation for over 12 hours to ensure prolonged gastric residence. [52]

Swelling Index and Water Uptake

In swelling-based GRDDS, the ability of the dosage form to increase in size upon contact with gastric fluids is essential for gastric retention. The swelling of the polymers can be measured by their ability to absorb water and swell. Water uptake studies of the formulation are performed using USP dissolution apparatus II. The medium used is usually distilled water or 0.1 N HCl (900mL) rotated at 50 rpm and maintained at 37 ± 0.5°C throughout the study. After a selected time interval, the formulation is withdrawn, blotted to remove excess water, and weighed. [53, 54] For significant gastroretentive behavior, formulations should exhibit a swelling index above 150% within 2–3 hours. [55] Swelling characteristics of the tablets expressed in terms of water (WU) are calculated as:

Swelling Index (%) = $[(W_t - W_0) / W_0] \times 100$
Where,

W_t is the weight at time t

W_0 is the initial weight.

Density (Specific Gravity)

For a floating system to remain buoyant in the stomach, its density must be less than that of gastric fluids (approximately 1.004 g/cm³) while that for high density systems should be more than this, so the dosage form sinks at the bottom of stomach. Systems with a density below 0.9 g/cm³ typically achieve rapid and sustained buoyancy while an increase in density of the dosage form greater than 2.500 g/cm^3 enhances the gastric retention time of the dosage form. Density can be determined by the displacement method using Benzene displacement medium. [56, 57]

Hardness and Friability

Mechanical strength testing ensures that the dosage form retains its integrity during gastric retention. Tablet hardness should typically exceed 5 kg/cm² to withstand gastric motility, while friability should be less than 1% weight loss after 100 rotations in a friabilator. [58]

In Vitro Drug Release Studies

The sustained release profile is critical in GRDDS to maintain therapeutic drug levels. In vitro drug release from GRDDS is commonly evaluated using the United States Pharmacopeia (USP) Type II (paddle) dissolution apparatus operated at 37 ± 0.5°C, which simulates physiological body temperature. The dissolution medium typically consists of 900 mL of 0.1 N hydrochloric acid (HCl), mimicking the gastric environment. Sampling is performed at predefined intervals to generate a release profile, which is then analyzed using mathematical models. Ideal GRDDS formulations aim to exhibit zero-order kinetics, where the drug is released at a constant rate regardless of concentration, or Higuchi kinetics, which describe release based on diffusion through a matrix. [59]

In Vivo Gastric Retention Studies

In vivo studies are crucial to confirm how long a gastroretentive dosage form actually stays in the stomach after administration. Techniques such as gamma scintigraphy, X-ray imaging with radio-opaque markers, and MRI are commonly used to track the position of the dosage form in real time. Among these, gamma scintigraphy is often

preferred for its accuracy and non-invasiveness [60]. An effective GRDDS is typically expected to remain in the stomach for more than 6 hours to ensure sustained drug release at the site of absorption [61]. Factors like gastric motility, food intake, and body position can influence these outcomes, highlighting the need for in vivo validation alongside in vitro assessments. [59]

Bioadhesive Strength (For Mucoadhesive GRDDS)

For mucoadhesive systems, the adhesive force to the gastric mucosa is crucial. This is measured using modified balance or texture analyzers. Bioadhesive strength of a polymer can be determined by measuring the force required to separate a polymer specimen sandwiched between layers of either an artificial (e.g. cellophane) or a biological (e.g. rabbit stomach tissue) membrane. This force can be measured by using a modified precision balance or an automated texture analyzer. A minimum detachment force of 0.5 N is generally considered acceptable for gastric retention. [62, 63]

Challenges And Limitations

Despite the therapeutic advantages of GRDDS in improving the bioavailability and plasma concentration consistency of cardiovascular drugs, several formulation challenges persist. The primary challenge in developing GRDDS is ensuring the system remains in the stomach or the upper small intestine long enough to release the drug at a controlled rate. Gastric emptying time varies significantly and is influenced by factors such as the physical nature of the dosage form and whether the stomach is in a fed or fasted state. Generally, gastric retention is longer when the stomach is fed and shorter during fasting. [64] Other factors including the type and caloric content of food, as well as individual characteristics like age and gender also affect gastric emptying. [65] High-fat meals, for example, significantly delay gastric emptying, and certain indigestible polymers or fatty acid salts can alter stomach motility to further reduce emptying rates. [66] Other factors such as the size and shape of the dosage form, a patient's disease state, and body mass index further impact gastric residence time and, consequently, drug efficacy. [67] Notably, multiple-unit GRDDS often offer more consistent and predictable drug release than single-unit systems, which may leave the stomach before becoming effective due to the interplay between lag time and gastric emptying. [6] Floating systems may also pose a risk of dose dumping, especially for drugs with a narrow therapeutic index, such as isosorbide mononitrate, where uncontrolled release can lead to serious cardiovascular side effects. These challenges necessitate careful optimization of drug release kinetics, buoyancy, matrix stability, and patient adherence to fully realize the potential of GRDDS in cardiovascular therapy.

Future Perspective

Although various gastroretentive drug delivery systems (GRDDS) have been developed, many still face limitations particularly inconsistent gastric retention times (GRT) influenced by fed and fasted states. Since no single system fully addresses these challenges, combining multiple mechanisms such as floating with mucoadhesive, expandable, or high-density features offers a more reliable solution. These dual-function systems are less affected by physiological variations and can better maintain prolonged gastric residence. Future GRDDS for cardiovascular drugs are likely to evolve through innovative materials and smart technologies. Polymers with pH-responsive, mucoadhesive, and biodegradable properties can improve both retention and drug release profiles. Integration of stimuli-responsive hydrogels,

expandable systems, or magnetically controlled devices could enable adaptive drug delivery aligned with circadian rhythms of cardiovascular symptoms. Personalized approaches, informed by pharmacogenomics and digital health monitoring, may further refine treatment. To support clinical translation, future work should focus on scalable manufacturing, improved in vitro-in vivo correlation models, and non-invasive tools for real-time tracking of drug behavior in the stomach.

CONCLUSION

Gastroprotective drug delivery systems have emerged as a valuable solution for addressing the pharmacokinetic limitations of cardiovascular drugs, particularly those with narrow absorption windows, short half-lives, and extensive first-pass metabolism. The successful formulation of cardiovascular drugs such as propranolol, atenolol, diltiazem, losartan, and others into GRDDS has demonstrated significant improvements in therapeutic outcomes. These systems offer sustained drug release profiles, reduced dosing frequency, and enhanced patient compliance, which are particularly crucial for chronic cardiovascular conditions requiring consistent plasma drug concentrations. However, the field still faces challenges related to unpredictable gastric emptying times influenced by physiological factors such as fed/fasted states, food composition, and individual patient characteristics. The variability in gastric retention times remains a significant hurdle that affects the reliability and predictability of drug release from GRDDS. Future developments in GRDDS are likely to focus on dual-mechanism systems that combine multiple retention strategies to overcome single-system limitations. The integration of smart polymers with stimuli-responsive properties, along with personalized medicine approaches incorporating pharmacogenomics and digital health monitoring, represents the next frontier in gastroretentive drug delivery.

REFERENCES

1. Nayak AK, Malakar J, Sen KK. Gastroretentive drug delivery technologies: Current approaches and future potential. Journal of Pharmaceutical Education and Research. 2010;1(2):1.
2. Das S, Kaur S, Rai VK. Gastro-retentive drug delivery systems: a recent update on clinical pertinence and drug delivery. Drug Deliv Transl Res. 2021;11(5):1849-77.
3. Lopes CM, Bettencourt C, Rossi A, Buttini F, Barata P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. Int J Pharm. 2016;510(1):144-58.
4. Zhao S, Lv Y, Zhang JB, Wang B, Lv GJ, Ma XJ. Gastroretentive drug delivery systems for the treatment of Helicobacter pylori. World J Gastroenterol. 2014;20(28):9321-9.
5. Patel RI, Shah C, Chauhan N, Upadhyay U. Gastro-retentive drug delivery systems: Modern insights on approaches and applications. Int J Gastrointest Interv. 2025;14(2):43-50.
6. Prinderre P, Christophe S, and Fuxen C. Advances in gastro retentive drug-delivery systems. Expert Opinion on Drug Delivery. 2011;8(9):1189-203.
7. Boldhane SP, Kuchekar BS. Development and optimization of metoprolol succinate gastroretentive drug delivery system. Acta Pharm. 2010;60(4):415-25.
8. Garg R, Gupta G. Progress in controlled gastroretentive delivery systems. Tropical journal of pharmaceutical research. 2008;7(3):1055-66.
9. Venkata Srikanth M, Sreenivasa Rao N, Ambedkar Sunil S, Janaki Ram B, Kolapalli VRM. Statistical design and evaluation of a

propranolol HCl gastric floating tablet. Acta Pharmaceutica Sinica B. 2012;2(1):60-9.
10. Borg TM, El-Dahan MS, Hammoodi HA. Bioavailability Improvement of Diltiazem Hydrochloride Gastroretentive Sustained Release Tablets. Journal of Pharmacy and Biological Sciences. 2016;11(6):44-52.
11. Sabale V, Sakarkar S, Pund S, Sabale P. Formulation and Evaluation of Floating Dosage Forms: An Overview. Systematic Reviews in Pharmacy. 2010;1(1).
12. Kurniawan DW, Triyanto DA, Utami VVFR. Sustained release of captopril tablet with floating system using a cross-linked matrix of alginate. Kartika: Jurnal Ilmiah Farmasi. 2018;6(1):11-20.
13. More S, Gavali K, Doke O, Kasgawade P. GASTRORETENTIVE DRUG DELIVERY SYSTEM. Journal of Drug Delivery and Therapeutics. 2018;8(4):24-35.
14. Khalaf M, Alinejad S, Sajad O, Rasool BA. Gastro-retentive drug delivery technologies and their applications with cardiovascular medications. J Popul Ther Clin Pharmacol. 2023;30(5):1-19.
15. Klausner EA, Eyal S, Lavy E, Friedman M, Hoffman A. Novel levodopa gastroretentive dosage form: in-vivo evaluation in dogs. J Control Release. 2003;88(1):117-26.
16. Jagdale SC, Agavekar AJ, Pandya SV, Kuchekar BS, Chabukswar AR. Formulation and evaluation of gastroretentive drug delivery system of propranolol hydrochloride. AAPS PharmSciTech. 2009;10(3):1071-9.
17. N. Abed H, A. Abdulrasool A, M. Ghareeb M. Controlled Release Floating Matrix Tablet of Captopril. Iraqi Journal of Pharmaceutical Sciences. 2017;20(2):1-8.
18. Streubel A, Juergen S, and Bodmeier R. Gastroretentive drug delivery systems. Expert Opinion on Drug Delivery. 2006;3(2):217-33.
19. Boddupalli BM, Mohammed ZN, Nath RA, Banji D. Mucoadhesive drug delivery system: An overview. Journal of advanced pharmaceutical technology & research. 2010;1(4):381-7.
20. Whitehead L, Fell J, Collett J, Sharma H, Smith A-M. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. Journal of controlled release. 1998;55(1):3-12.
21. Joseph N, Lakshmi S, Jayakrishnan A. A floating-type oral dosage form for piroxicam based on hollow polycarbonate microspheres: in vitro and in vivo evaluation in rabbits. Journal of controlled release. 2002;79(1-3):71-9.
22. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. International journal of pharmaceutics. 1996;136(1-2):117-39.
23. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. Pharmaceutical research. 1997;14:815-9.
24. Zanke AA, Gangurde HH, Ghonge AB, Chavan PS. Recent Advance in Gastroretantive Drug Delivery System (GRDDS). Asian Journal of Pharmaceutical Research. 2022;12(2):143-9.
25. Raghu Kiran CVS, Gopinath C. Development and evaluation of interpenetrating polymer network based superporous hydrogel gastroretentive drug delivery systems (SPH IPN-GRDDS). Materials Today: Proceedings. 2021;46:3056-61.
26. Bardonnet P, Faivre V, Pugh W, Piffaretti J, Falson F. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. Journal of controlled release. 2006;111(1-2):1-18.

27. Co A, Mu U. A Comparative Study Of Floating Drug Delivery System Of Metronidazole Formulated Using Effervescent And Non-Effervescent Techniques. Journal of Pharmaceutical & Allied Sciences. 2019;16(3).
28. El Nabarawi MA, H. TM, A. AE-MR, A. ENN, and Gaber DA. Formulation, release characteristics, and bioavailability study of gastroretentive floating matrix tablet and floating raft system of Mebeverine HCl. Drug Design, Development and Therapy. 2017;11(null):1081-93.
29. Hasnain MS, Rishishwar P, Ali S. Floating-bioadhesive matrix tablets of hydralazine HCL made of cashew gum and HPMC K4M. Int J Pharm Pharm Sci. 2017;9(7):124-9.
30. Goswami DS, Sharma M. Amoxicillin Mucoadhesive Tablet: Formulation and Characterization. World Journal Of Pharmacy And Pharmaceutical Sciences. 2013;2(2):629-35.
31. Sogias IA, Williams AC, Khutoryanskiy VV. Chitosan-based mucoadhesive tablets for oral delivery of ibuprofen. International journal of pharmaceutics. 2012;436(1-2):602-10.
32. Khandai M, Chakraborty S, Sharma A, Panda D, Khanam N, Panda SK. Development of propranolol hydrochloride matrix tablets: An investigation on effects of combination of hydrophilic and hydrophobic matrix formers using multiple comparison analysis. Int J Pharm Sci. 2010;1(2):1-7.
33. Liang Y-K, Cheng W-T, Chen L-C, Sheu M-T, Lin H-L. Development of a Swellable and Floating Gastroretentive Drug Delivery System (sfGRDDS) of Ciprofloxacin Hydrochloride. Pharmaceutics. 2023;15(5):1428.
34. Kumar R, Philip A. Gastroretentive Dosage Forms for Prolonging Gastric Residence Time. International Journal of Pharmaceutical Medicine. 2007;21(2):157-71.
35. Mandel, Daggy, Brodie, Jacoby. Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. Alimentary Pharmacology & Therapeutics. 2000;14(6):669-90.
36. Rodrigues GS, Barboza JM, Buranello LP, Brandão VM, Ferrari PC, Soares GA, et al. In Vitro and In Vivo Evaluation of Magnetic Floating Dosage Form by Alternating Current Biosusceptometry. Pharmaceutics. 2024;16(3):351.
37. Uboldi M, Arianna C, Margherita R, Francesco B-V, Alice M, and Zema L. Development of a multi-component gastroretentive expandable drug delivery system (GREDDS) for personalized administration of metformin. Expert Opinion on Drug Delivery. 2024;21(1):131-49.
38. Chen J, Park K. Synthesis and characterization of superporous hydrogel composites. Journal of controlled release. 2000;65(1-2):73-82.
39. Navaneetha K. Formulation and Evaluation of Gastro Retentive Floating Tablets of Atenolol. 2014;4.
40. Gunda RK. Design, Formulation and Evaluation of Atenolol Gastro Retentive Floating Tablets. Asian Journal of Pharmaceutics (AJP). 2016;9(4).
41. Swain R, Pendela S, Panda S. Formulation and evaluation of gastro-bilayer floating tablets of simvastatin as immediate release layer and atenolol as sustained release layer. Indian J Pharm Sci. 2016;78(4):458-68.
42. Chandira M, Chandramohan D, Chiranjib BJ, Kumar K. Design and characterization of sustained release gastro retentive floating tablets of Diltiazem hydrochloride. Sch Res Libr Der Pharm Lett. 2009;1:25-38.
43. Kalidindi DV. Microspheres of Diltiazem hydrochloride by ionotropic gelation

technique. International Journal of Pharmaceutical Sciences and Research. 2017;8(3):1413.
44. Rahamathulla M, Saisivam S, Alshetaili A, Hani U, Gangadharappa HV, Alshehri S, et al. Design and Evaluation of Losartan Potassium Effervescent Floating Matrix Tablets: In Vivo X-ray Imaging and Pharmacokinetic Studies in Albino Rabbits. Polymers. 2021;13(20):3476.
45. Getyala A, V. Gangadharappa H, Sarat Chandra Prasad M, Praveen Kumar Reddy M, M. Pramod Kumar T. Formulation and evaluation of non-effervescent floating tablets of losartan potassium. Current drug delivery. 2013;10(5):620-9.
46. Rao K, Prakash K, B B, Prasad K, Madhavi C, Gobinath M. Formulation and evaluation of gastro-retentive drug delivery system of losartan potassium by using raft-forming approach. International Journal of Research in Pharmaceutical Sciences. 2015;6:204-12.
47. Varshi R, Jain V, Pal P, Gehlot N. Formulation and Evaluation of Extended Release Gastroretentive Tablets of Metroprolol Succinate. Journal of Drug Delivery & Therapeutics. 2022;12.
48. Raza A, Hayat U, Wang H-J, Wang J-Y. Preparation and evaluation of captopril loaded gastro-retentive zein based porous floating tablets. International Journal of Pharmaceutics. 2020;579:119185.
49. Mukherjee B, Mahanti B, Panda P, Mahapatra S. Preparation and evaluation of verapamil hydrochloride microcapsules. Am J Ther. 2005;12(5):417-24.
50. Rao KRK, Lakshmi KR. Design, development and evaluation of clopidogrel bisulfate floating tablets. International journal of pharmaceutical investigation. 2014;4(1):19.
51. Hilton A, Deasy P. In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate. International Journal of pharmaceutics. 1992;86(1):79-88.
52. Turac IR, Porfire A, Iurian S, Crișan AG, Casian T, Iovanov R, et al. Expanding the Manufacturing Approaches for Gastroretentive Drug Delivery Systems with 3D Printing Technology. Pharmaceutics. 2024;16(6).
53. Rouge N, Cole ET, Doelker E, Buri P. Buoyancy and drug release patterns of floating minitablets containing piretanide and atenolol as model drugs. Pharmaceutical development and technology. 1998;3(1):73-84.
54. Prajapati R, Kumar B, Sahoo J, Shakya S, Lal DK. Quality by design approach for the formulation of bilayer tablets of domperidone and itopride in gastro-esophageal reflux disease. Journal of Applied Pharmaceutical Science. 2024;14(8):169-81.
55. Hossain M, Banik S, Moghal M, Bhatta R. Swelling and mucoadhesive behavior with drug release characteristics of gastoretentive drug delivery system based on a combination of natural gum and semi-synthetic polymers. Marmara Pharmaceutical Journal. 2018;22:286-98.
56. Clarke G, Newton J, Short M. Gastrointestinal transit of pellets of differing size and density. International journal of pharmaceutics. 1993;100(1-3):81-92.
57. Tripathi J, Thapa P, Maharjan R, Jeong SH. Current State and Future Perspectives on Gastroretentive Drug Delivery Systems. Pharmaceutics. 2019;11(4):193.
58. Blaesi AH, Kümmerlen D, Richter H, Saka N. Mechanical strength and gastric residence time of expandable fibrous dosage forms. Int J Pharm. 2022;613:120792.
59. Schneider F, Koziolek M, Weitschies W. In Vitro and In Vivo Test Methods for the Evaluation of Gastroretentive Dosage Forms. Pharmaceutics. 2019;11(8).

60. Sharif H, Devadason D, Abrehart N, Stevenson R, Marciani L. Imaging Measurement of Whole Gut Transit Time in Paediatric and Adult Functional Gastrointestinal Disorders: A Systematic Review and Narrative Synthesis. Diagnostics (Basel). 2019;9(4).
61. Vinchurkar K, Sainy J, Khan MA, Mane S, Mishra DK, Dixit P. Features and Facts of a Gastroretentive Drug Delivery System-A Review. Turk J Pharm Sci. 2022;19(4):476-87.
62. Ponchel G, Irache J-M. Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. Advanced drug delivery reviews. 1998;34(2-3):191-219.
63. Liu Z, Lu W, Qian L, Zhang X, Zeng P, Pan J. In vitro and in vivo studies on mucoadhesive microspheres of amoxicillin. Journal of controlled release. 2005;102(1):135-44.
64. Camilleri M, Iturrino J, Bharucha AE, Burton D, Shin A, Jeong ID, et al. Performance characteristics of scintigraphic measurement of gastric emptying of solids in healthy participants. Neurogastroenterology & Motility. 2012;24(12):1076-e562.
65. Shah S, Patel J, Patel N. Stomach specific floating drug delivery system: A review. Int J Pharm Tech Res. 2009;1(3):623-33.
66. Mudie DM, Amidon GL, Amidon GE. Physiological parameters for oral delivery and in vitro testing. Molecular pharmaceutics. 2010;7(5):1388-405.
67. Kong F, Singh RP. Modes of disintegration of solid foods in simulated gastric environment. Food biophysics. 2009; 4:180-90.

HOW TO CITE: Priti Kumari*, Amit Kumar, Gastroprotective Drug Delivery Systems and Their Role in Advancing Cardiovascular Therapeutics, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 6, 1507-1522. https://doi.org/10.5281/zenodo.15615932