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GASTRORETENTIVE DRUG DELIVERY OPTIMIZATION FOR CARDIOVASCULAR THERAPY

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ABSTRACT

Cardiovascular drugs with narrow absorption windows, short half-lives, pH-dependent solubility, or extensive first-pass metabolism often require frequent dosing to sustain therapeutic plasma concentrations. Gastroretentive drug delivery systems (GRDDS)—including floating, bioadhesive, density-modified, expandable, and superporous platforms—can prolong gastric residence time (GRT) and enhance absorption for such molecules. This paper synthesizes design principles and optimization strategies for GRDDS tailored to cardiovascular therapy, with an emphasis on Quality by Design (QbD) and Design of Experiments (DoE), physiologically-based rationale, critical material attributes (CMAs), and critical process parameters (CPPs). We outline formulation paths for representative cardiovascular agents (e.g., metoprolol, propranolol, losartan), analytical and in-vitro/in-vivo evaluation, in-silico performance modeling, and translational considerations. Finally, we highlight risks, regulatory expectations, and a decision framework that links drug–physiology–device interactions to robust, patient-centric gastroretentive products.

KEYWORDS: Gastroretentive drug delivery system (GRDDS), cardiovascular therapy, gastric residence time, floating tablets, mucoadhesive systems.

I. INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, necessitating long-term and consistent pharmacological intervention to control blood pressure, heart rate, vascular tone, and other critical parameters related to cardiac function. The pharmacotherapy of cardiovascular disorders often involves drugs with short biological half-lives, narrow absorption windows, variable bioavailability, and extensive first-pass

metabolism. Examples include β-blockers such as metoprolol and propranolol, ACE inhibitors like captopril, certain calcium channel blockers, and angiotensin receptor blockers with solubility-limited absorption. Traditional oral dosage forms for such drugs may result in frequent dosing requirements, peak–trough plasma fluctuations, and suboptimal therapeutic effects. Furthermore, poor adherence to multi-dose regimens, especially in chronic conditions like hypertension or heart failure, can lead to inadequate disease control and an increased risk of acute events. This scenario has spurred the need for innovative delivery strategies that can optimize pharmacokinetic profiles, reduce dosing frequency, and enhance patient compliance. Gastroretentive drug delivery systems (GRDDS) have emerged as a promising solution for such therapeutic challenges by prolonging gastric residence time (GRT) and enabling sustained drug release in the upper gastrointestinal (GI) tract, thereby improving bioavailability and clinical outcomes.

The rationale for gastroretentive systems in cardiovascular therapy is grounded in the physiological and biopharmaceutical characteristics of certain drugs. Many cardiovascular agents exhibit optimal absorption in the stomach or proximal small intestine due to favorable pH conditions, high surface area, and abundant perfusion. For such drugs, rapid gastric emptying into the distal intestine can significantly limit absorption and therapeutic efficiency. GRDDS are engineered to remain in the stomach for extended periods—typically 6 to 12 hours—allowing the drug to be released gradually and absorbed efficiently before being transported to less favorable absorption sites. This is particularly advantageous for drugs with solubility that is pH-dependent, acid-stable molecules, and those that demonstrate a positive food effect. By modulating drug release kinetics and synchronizing them with the absorptive capacity of the upper GI tract, gastroretentive systems can maintain therapeutic plasma levels for longer durations, potentially lowering the total daily dose and reducing side effects related to peak plasma concentrations.

The design of gastroretentive systems for cardiovascular therapy requires careful consideration of multiple interdependent factors, including drug physicochemical properties, gastric physiology, and patient variability. The drug's pKa, solubility, stability in acidic conditions, permeability, and dose size are pivotal determinants of suitability for gastroretentive delivery. Similarly, understanding gastric motility patterns, the influence of fed and fasted states on GRT, and the mechanical and chemical environment of the stomach is crucial for formulation success. Different technological platforms—such as floating systems, bioadhesive

formulations, swelling or expandable devices, high-density systems, and superporous hydrogels—offer distinct retention mechanisms, each with its own benefits and limitations in the cardiovascular context. Floating systems, for instance, reduce gastric emptying by maintaining buoyancy on gastric fluids, while mucoadhesive systems attach to the gastric mucosa, resisting peristaltic clearance. Hybrid designs that combine multiple mechanisms often yield superior performance in variable physiological conditions.

In recent years, formulation optimization for GRDDS has been revolutionized by the application of Quality by Design (QbD) principles and Design of Experiments (DoE) methodologies. QbD facilitates a systematic approach to product development by defining a Quality Target Product Profile (QTPP), identifying Critical Quality Attributes (CQAs), and linking them to Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs). In cardiovascular applications, where the therapeutic index may be narrow and patient adherence is critical, these optimization strategies allow for robust, reproducible, and patient-centric product design. Floating lag time, total floating duration, swelling index, matrix integrity, and in-vitro drug release kinetics are common CQAs in GRDDS intended for cardiovascular drugs. By adjusting polymer type and viscosity, effervescent agent concentration, tablet hardness, and other formulation variables through factorial or response surface designs, developers can fine-tune the release profile to meet therapeutic needs while maintaining manufacturability and stability.

Clinical evidence supports the potential benefits of gastroretentive delivery in cardiovascular therapy. For example, metoprolol succinate, when formulated in a floating sustained-release tablet, demonstrates smoother plasma concentration–time curves, reduced fluctuation index, and improved 24-hour coverage compared to conventional dosage forms. This not only enhances blood pressure and heart rate control but also minimizes dose-dependent adverse effects like bradycardia or hypotension. In addition, the reduced dosing frequency associated with GRDDS can significantly improve adherence, a critical factor in the long-term management of chronic cardiovascular conditions. Poor adherence to cardiovascular medication regimens has been consistently linked to worsened outcomes, including increased hospitalizations and mortality, highlighting the clinical importance of delivery systems that simplify treatment schedules.

Despite their promise, gastroretentive systems for cardiovascular therapy face several challenges. Physiological variability in gastric emptying time, particularly between individuals

and in response to food intake, can affect retention and drug release. Moreover, patient-specific factors such as age, comorbid conditions (e.g., diabetic gastroparesis), and concurrent medication use can alter gastric motility and pH, impacting GRDDS performance. Formulations must also meet regulatory standards for safety, particularly in ensuring that retention mechanisms do not cause gastric obstruction or irritation. Advanced in-vitro–in-vivo correlation (IVIVC) models, gamma scintigraphy, and smart capsule telemetry are increasingly used to assess and predict in-vivo behavior, enabling the fine-tuning of formulations for consistent clinical performance.

In gastroretentive drug delivery offers a compelling strategy for optimizing cardiovascular pharmacotherapy, particularly for drugs with narrow absorption windows, short half-lives, and pH-dependent solubility profiles. By prolonging gastric residence and controlling release kinetics, these systems can improve bioavailability, reduce dosing frequency, and enhance patient adherence—key factors in achieving sustained therapeutic benefit in chronic cardiovascular diseases. The integration of advanced formulation science, predictive modeling, and patient-centric design principles ensures that GRDDS will continue to play a transformative role in the future of cardiovascular therapy. Ongoing research into novel materials, hybrid retention mechanisms, and digital health integration promises to further refine and personalize these delivery systems, maximizing their clinical impact in an era of precision medicine.

II. CANDIDATE SELECTION & MECHANISTIC RATIONALE

The success of gastroretentive drug delivery systems (GRDDS) in cardiovascular therapy depends heavily on the careful selection of candidate drugs based on their physicochemical and biopharmaceutical characteristics, as well as an in-depth understanding of gastric physiology. Not every cardiovascular drug is an ideal candidate for GRDDS, and the suitability must be established by evaluating parameters such as absorption window, half-life, solubility, pH stability, permeability, dose size, and metabolic profile. The fundamental mechanistic rationale behind GRDDS is to prolong the gastric residence time (GRT) so that drugs absorbed preferentially in the stomach or upper small intestine can be released and absorbed before the dosage form is emptied into distal regions of the gastrointestinal tract, where absorption may be poor or negligible.

From a drug-centric perspective, one of the primary selection criteria is the **absorption window**. Many cardiovascular drugs, such as metoprolol, propranolol, captopril, and certain dihydropyridines, are absorbed more efficiently in the duodenum and proximal jejunum due to favorable pH, high vascularity, and optimal transporter activity. If such drugs pass too quickly into the lower intestine, bioavailability can be significantly reduced. GRDDS mitigates this by retaining the dosage form in the stomach, releasing the drug gradually in proximity to its optimal absorption site. Another important criterion is the **biological half-life**. Drugs with short half-lives (typically less than 6–8 hours) benefit most from gastroretentive sustained-release formulations, as these systems can provide controlled input over extended periods, reducing dosing frequency and maintaining therapeutic plasma levels.

Solubility and pH stability also play critical roles in candidate selection. Drugs that are highly soluble in acidic pH, such as certain β-blockers and calcium channel blockers, are prime candidates because the acidic environment of the stomach enhances their dissolution and absorption. Acid-stable drugs are preferred since the gastric pH can be as low as 1–2; acid-labile drugs would require additional protection, such as enteric layering within the gastroretentive device, which adds complexity. **Permeability** should also be sufficient to ensure that the extended release from the stomach translates into efficient systemic absorption.

From a physiology-centric perspective, the mechanistic rationale involves exploiting gastric retention mechanisms to synchronize drug release with optimal absorption conditions. This can be achieved through different approaches: floating systems that remain buoyant on gastric fluids due to low density, bioadhesive systems that adhere to the mucosal lining, swelling or expandable systems that resist passage through the pylorus, and high-density systems that sink and lodge in gastric folds. The choice of mechanism depends on drug properties and patient-related factors. For example, floating systems are effective in both fed and fasted states but are more predictable when administered postprandially due to delayed gastric emptying. Bioadhesive systems provide site-specific retention but must overcome the natural turnover of mucus and peristaltic forces.

Patient-specific variables such as gastric motility disorders, pH changes from proton pump inhibitor use, and comorbidities like diabetes (which may delay gastric emptying) must be accounted for during formulation design. Safety considerations are equally important, ensuring that the dosage form disintegrates or passes safely after the intended retention period to avoid gastric obstruction.

In selecting a cardiovascular drug for GRDDS requires a precise alignment between the drug's pharmacokinetic and physicochemical profile and the gastric retention mechanism employed. When this alignment is achieved, GRDDS can significantly enhance bioavailability, reduce dosing frequency, improve patient adherence, and optimize therapeutic outcomes in chronic cardiovascular disease management.

III. PHYSIOLOGY-CENTRIC FILTERS

When designing gastroretentive drug delivery systems (GRDDS) for cardiovascular therapy, understanding the physiological environment of the stomach is as critical as evaluating the drug's physicochemical properties. The stomach is a dynamic organ with complex motility patterns, variable pH, and fluctuating fluid volumes, all of which directly influence the gastric residence time (GRT) and, consequently, the performance of a gastroretentive formulation. **Physiology-centric filters** refer to the specific biological and mechanical conditions that determine whether a GRDDS can function effectively and safely in a given patient population. One of the most important physiological factors is **gastric motility**, which operates differently in the fed and fasted states. In the fasted state, the migrating motor complex (MMC) cycles every 90–120 minutes, producing strong peristaltic waves that sweep gastric contents rapidly into the duodenum. This limits the retention time of dosage forms that are not specifically designed to resist such clearance. In contrast, the fed state prolongs GRT due to delayed gastric emptying, particularly with meals rich in fats and proteins. Therefore, for many GRDDS—especially floating and swelling systems—administration with or after a meal is recommended to enhance retention and improve consistency of drug release.

Gastric pH is another critical variable. In healthy adults, fasting gastric pH typically ranges from 1.0 to 2.5, while fed-state pH may rise to 3.0–6.0 depending on meal composition. Many cardiovascular drugs intended for GRDDS are more soluble in acidic conditions, which supports their use in stomach-retentive systems. However, the widespread use of proton pump inhibitors (PPIs) or H_2 receptor antagonists, especially among elderly patients with cardiovascular disease, can elevate gastric pH and potentially reduce solubility-driven absorption. This must be considered in formulation design, often by incorporating solubilizing agents or pH modifiers.

Gastric fluid volume and viscosity also affect GRDDS performance. A sufficient volume of gastric fluid is necessary for buoyancy in floating systems and for proper swelling in

expandable hydrogels. In patients with reduced fluid intake or dehydration, swelling or floating mechanisms may be less reliable. Conversely, large fluid volumes may reduce adhesion strength in mucoadhesive systems, promoting early detachment.

Anatomical and patient-specific factors further influence GRDDS behavior. Conditions like diabetic gastroparesis or hypothyroidism can significantly prolong gastric emptying, which might enhance retention beyond intended limits—necessitating built-in safety mechanisms to ensure eventual disintegration or passage. On the other hand, hypermotility disorders, partial gastrectomy, or gastric bypass surgery can drastically shorten GRT, making gastroretentive approaches less feasible. Age, gender, body mass index (BMI), and the presence of comorbidities also modulate gastric transit patterns.

Finally, **safety considerations** must be addressed in relation to physiology. Retentive systems, especially expandable designs, must disintegrate or shrink after the desired period to avoid gastric obstruction, ulceration, or mucosal damage. Devices should be engineered with "fail-safe" mechanisms—such as timed polymer erosion or controlled structural collapse—aligned with the patient's physiological parameters.

In physiology-centric filters act as a reality check, ensuring that the gastroretentive concept is not only theoretically beneficial for the drug but also compatible with the diverse and sometimes unpredictable gastric environments of the target patient population. Aligning formulation design with these physiological variables is essential to achieving reliable, safe, and clinically effective gastroretentive delivery in cardiovascular therapy.

IV. PLATFORM CHOICES FOR CARDIOVASCULAR APIS

The design of gastroretentive drug delivery systems (GRDDS) for cardiovascular active pharmaceutical ingredients (APIs) requires careful platform selection to match drug properties with the appropriate gastric retention mechanism. Each platform employs a different strategy to overcome gastric emptying and maintain the dosage form in the stomach for a prolonged period, thereby improving the bioavailability and therapeutic effect of drugs with narrow absorption windows or pH-dependent solubility. For cardiovascular drugs—such as metoprolol, propranolol, captopril, amlodipine, isosorbide dinitrate, and certain statins—platform choice is dictated by physicochemical characteristics (solubility, pKa, stability), pharmacokinetic needs (half-life, absorption site), and patient-specific variables (gastric motility, comorbidities).

1. **Floating Drug Delivery Systems (FDDS)** Floating platforms are among the most widely used for cardiovascular APIs. They operate on the principle of buoyancy, where the dosage form's density is kept lower than that of gastric fluids (~1.004 g/cm³), enabling it to float on the stomach contents. This mechanism is especially suitable for APIs soluble in acidic pH and stable in gastric fluid. For example, metoprolol succinate and propranolol hydrochloride have been successfully formulated into floating tablets and capsules, providing sustained plasma levels and reducing dosing frequency. FDDS can be single-layer (non-effervescent) or effervescent, with gas-generating agents such as sodium bicarbonate producing CO_2 to enhance buoyancy. The main limitation is dependency on sufficient gastric fluid volume, making administration in the fed state preferable.
2. **Mucoadhesive (Bioadhesive) Systems** Mucoadhesive systems employ polymers such as carbomers, chitosan, or hydroxypropyl methylcellulose (HPMC) that bind to the gastric mucosa via non-covalent interactions (electrostatic forces, hydrogen bonding, van der Waals forces). This adhesion prolongs gastric residence, enabling site-specific release. Cardiovascular APIs like captopril, which have a short half-life and require rapid but sustained delivery in the upper GI tract, benefit from this approach. Mucoadhesive systems are less dependent on gastric fluid volume and motility patterns but may lose adhesion due to mucus turnover or peristalsis.
3. **Swelling and Expandable Systems** These platforms rely on polymers that swell upon contact with gastric fluids, increasing in size to prevent passage through the pyloric sphincter. Superporous hydrogels, cross-linked polyacrylic acids, and polyethylene oxide blends are common materials. Once expanded, the system can sustain drug release for 6–12 hours. This mechanism suits APIs like isosorbide dinitrate, which require controlled release to avoid tolerance development. The system must eventually break down into smaller fragments for safe passage, ensuring no risk of obstruction.
4. **High-Density Systems** In contrast to floating systems, high-density platforms sink in gastric fluids and remain in the lower part of the stomach. By using materials like barium sulfate or zinc oxide, the density is increased to >2.5 g/cm³, resisting peristaltic clearance. This approach is less common for cardiovascular APIs but can be considered for drugs with strong acid stability and minimal pH-dependent solubility issues.

5. **Hybrid Systems** Hybrid designs combine two or more mechanisms—e.g., floating plus mucoadhesion or swelling plus effervescence—to overcome physiological variability. For example, a propranolol floating–mucoadhesive tablet can maintain buoyancy while also adhering to mucosal surfaces, ensuring reliable retention across fed and fasted states. Such systems often yield the most predictable pharmacokinetics for cardiovascular drugs in diverse patient populations.

Overall, platform choice is not a one-size-fits-all decision—it must align drug physicochemical properties with the retention mechanism most compatible with the patient's gastric physiology and the therapeutic objectives. For many cardiovascular APIs, floating and hybrid systems dominate due to their proven clinical benefits, but mucoadhesive and swelling approaches provide valuable alternatives for specific cases.

V. CONCLUSION

Gastroretentive delivery is a powerful strategy to optimize cardiovascular pharmacotherapy when the API's biopharmaceutic profile and upper-GI physiology align. Success hinges on rational selection, hybrid platform design, and QbD-driven optimization supported by DoE, mechanistic dissolution, and in-vivo validation. When thoughtfully executed, GRDDS can smooth exposure, extend dosing intervals, and improve adherence—translating to better control of blood pressure and heart rate with a safety-first posture.

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