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A Comprehensive Review on Raft-Forming Systems: An Advanced Strategy for Gastroretentive Drug Delivery

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Abstract

Gastroretentive raft-forming systems represent an advanced approach in drug delivery aimed at prolonging the residence time of pharmaceutical agents in the stomach. This strategy is crucial for enhancing oral bioavailability, particularly for drugs absorbed in the upper gastrointestinal tract, those with narrow absorption windows, or drugs requiring localized action. The core mechanism involves the interaction of effervescent excipients and gel-forming polymers, typically sodium alginate and gas-generating agents like sodium bicarbonate, within the gastric fluid. This interaction leads to the rapid formation of a cohesive, buoyant gel that floats on the stomach contents, trapping carbon dioxide and maintaining a density lower than gastric fluid. This floating raft acts as a physical barrier against gastric reflux and ensures the sustained release of the drug. These systems are specifically designed for the treatment of various gastrointestinal disorders, including gastroesophageal reflux disorder, acid reflux, peptic ulcers, and esophagitis. The development of successful raft-forming systems relies on comprehensive evaluation parameters, including in vitro gelling and buoyancy studies to confirm gel formation and floating characteristics, viscosity and density measurements to assess physical properties, and gel strength and raft resilience tests for mechanical integrity. Furthermore, drug content, acid neutralization capacity, and in vitro dissolution studies are vital for ensuring drug efficacy and controlled release. While challenges such as inter-subject variability in gastric physiology and manufacturing scalability exist, continuous advancements in materials science and fabrication techniques, such as 3D printing and nanoparticle encapsulation, are optimizing these innovative drug delivery systems for improved therapeutic outcomes.

Keywords: Raft-forming systems, Gastroretentive drug delivery, Gastric residence time, Oral bioavailability, *In vitro* evaluation, Drug release kinetics.

Introduction

Raft-forming systems are an advanced approach in drug delivery designed to extend the time pharmaceutical agents remain in the stomach, thereby boosting their effectiveness and how much of the drug is absorbed [1]. These systems achieve this by creating a thick, cohesive gel that floats on gastric fluids due to its low density. This floating layer acts as a physical barrier against reflux and ensures the drug is released steadily over time [1]. Such a mechanism is particularly useful for drugs absorbed in the upper gastrointestinal tract, those with a narrow absorption window, or drugs intended for local action within the stomach or esophagus [2].

Mechanism of Raft Formation

The fundamental principle behind raft formation involves the interaction of effervescent excipients and gel-forming polymers with stomach fluid. This interaction leads to the creation of a continuous, buoyant layer [3]. Buoyancy is typically achieved through the generation of carbon dioxide, which gets trapped within a hydrocolloid matrix, effectively lowering the system's overall density [4]. When these systems come into contact with gastric acid, a rapid production of CO_2 gas occurs, leading to the formation of a foaming gel, often made with sodium alginate (Figure 1), that floats on the stomach contents [1]. This sustained contact with the gastric mucosa can be beneficial for drugs requiring site-specific absorption or prolonged exposure in the stomach [1].

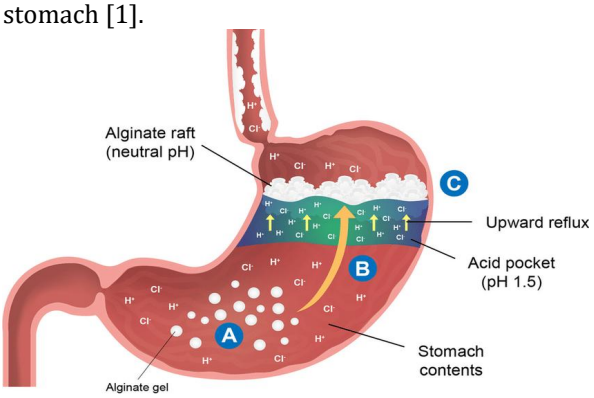

Figure 1: Mechanism of Raft Formation of alginate based raft forming system

Components and Factors Influencing Raft Formation

Natural polymers like alginic acid and chitosan, along with synthetic polymers such as hydroxypropyl methylcellulose, are commonly used to facilitate raft formation and optimize drug release [5]. The buoyancy of these systems often relies on effervescent agents like sodium bicarbonate and acid neutralizers, which allow them to remain in the stomach for an extended period, optimizing drug dissolution and absorption [6,7]. This prolonged gastric residence is especially valuable for antihypertensive drugs that have pH-dependent solubility or a limited absorption window in the upper GI tract, ensuring more consistent drug plasma levels [8].

The incorporation of gas-generating agents, such as sodium bicarbonate and calcium carbonate, together with raft-forming polymers like sodium alginate, ensures the immediate formation of a buoyant gel layer upon contact with gastric fluid [1]. This extended retention in the stomach, which can exceed 12 hours, allows for a more controlled drug release profile and improved bioavailability [1,8]. The buoyancy is primarily attributed to the CO2 produced by alkaline bicarbonates or carbonates reacting with gastric acid, which then becomes entrapped within a gel-forming matrix, typically containing alginate [9,10]. This trapped gas significantly reduces the formulation's bulk density, enabling it to float and prolong its residence time [11].

The interplay between effervescent components and hydrophilic polymers, such as HPMC and sodium alginate, is critical for achieving a rapid floating lag time and sustained drug release characteristics [8,9]. For instance, formulations integrating HPMC and Carbopol with sodium bicarbonate have successfully created robust floating matrices [12]. The concentration of sodium bicarbonate is crucial for minimizing floating lag time and maintaining buoyancy, as it produces CO2 bubbles trapped within the swollen polymer matrix [13]. This entrapment is further enhanced by the formation of a viscous gel layer around the tablet, which captures the gas and reduces density, promoting buoyancy [14].

Optimizing these effervescent systems involves balancing the amount of gas-forming agents to achieve quick buoyancy without compromising the raft's structural integrity or the drug's sustained release properties (Figure 2) [15]. The presence of sodium bicarbonate in an optimal ratio with acidic components like citric acid is essential for inducing effervescence and increasing the tablet's porosity, thereby enhancing floating capabilities and prolonging gastric residence [16]. The entrapped CO_2, facilitated by agents like HPMC K100 M, significantly reduces the tablet's density below unity, ensuring efficient floating [17]. Studies also indicate that a lower compression force during manufacturing can lead to shorter floating lag times [7]. The type and concentration of polymers, such as higher molecular weight HPMC grades, impact floating characteristics by promoting more robust gel formation and sustained buoyancy [18,19]. The judicious selection and optimal concentrations of excipients, such as Gelucire 43/01 as a release-retarding agent and HPMC K4M as a matrixing agent, further refine sustained release and overall gastric retention [20]. For example, an optimal sodium bicarbonate to citric acid ratio of 1:0.5 w/w has been identified for robust floating characteristics while maintaining tablet integrity [21]. This balance directly affects floating lag time, where increased gas-generating agents can decrease lag time but an excess may compromise matrix strength [14,22,23]. The inclusion of citric acid ensures a sufficiently acidic environment for sodium bicarbonate to react effectively, especially under fed conditions where gastric pH is elevated [24].

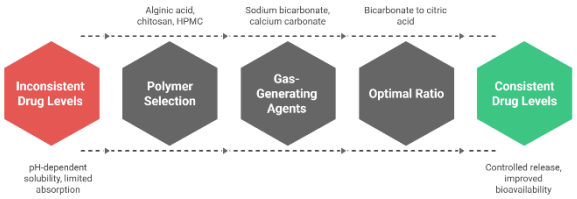

Figure 2: Optimizing drug release from raft forming system

Advantages of Raft-Forming Systems

Gastroretentive raft-forming systems offer significant benefits by prolonging the residence time of drugs in the gastric region. This extended retention is particularly advantageous for enhancing the oral bioavailability of drugs, especially those absorbed primarily in the stomach or upper small intestine [25,26]. By remaining in the stomach for several hours, these systems can improve drug solubility and absorption, leading to enhanced therapeutic efficacy and potentially more consistent plasma drug levels [8,25]. They are also crucial for drugs that require site-specific action within the stomach, addressing limitations of conventional drug delivery systems [27].

Broader Classification of Gastroretentive Drug Delivery Systems

While raft-forming systems are a prominent type of gastroretentive drug delivery system, they fall under a broader classification of technologies designed to prolong gastric residence time. These systems are crucial for enhancing drug bioavailability, particularly for drugs with a narrow absorption window in the upper gastrointestinal tract [28,29]. Beyond the floating mechanism characteristic of raft systems, GRDDS encompass several other innovative approaches, including:

- **Floating Systems:** These systems, including raft-forming systems, achieve gastric retention by maintaining a bulk density lower than that of gastric fluids, allowing them to remain buoyant in the stomach [27,30].
- **Mucoadhesive Systems:** These systems adhere to the gastric mucosa, thereby prolonging their residence time in the stomach [29,31].
- **Expandable and Swelling Systems:** These dosage forms increase significantly in size after administration, preventing their passage through the pylorus and retaining them in the stomach [29,32,33].
- **High-Density Systems:** These systems are designed to sink and reside at the bottom of the stomach, resisting gastric emptying [29,32].
- **Magnetic Systems:** These rely on external magnetic fields to retain dosage forms containing magnetic particles in the stomach [29].
- **Ion-Exchange Resin Systems:** These systems utilize ion-exchange properties to bind with gastric components, extending retention [29].

These diverse approaches aim to overcome issues like short gastric residence time, unpredictable gastric emptying, and poor bioavailability often encountered with conventional oral dosage forms [33].

Advanced Fabrication Techniques

Recent advancements in materials science and pharmaceutical engineering have paved the way for more precise and effective GRDDS. Modern fabrication techniques are being explored to modulate drug release kinetics and retention properties, addressing existing challenges [26]. These include:

- **3D Printing:** This additive manufacturing technology allows for the creation of complex geometries and personalized dosage forms with tailored release profiles and specific gastric retention characteristics [26].
- **Spray Drying:** A technique used to produce dry powders from a liquid or slurry, it can be employed to create microparticles or nanoparticles for GRDDS, offering control over particle size and morphology [26].
- **Nanoparticle Encapsulation:** Encapsulating drugs within nanoparticles can provide sustained therapeutic levels by modulating release kinetics and boosting effectiveness, which can be integrated into GRDDS for enhanced drug delivery [26].

Specific Drug Applications and Therapeutic Benefits

Gastroretentive systems are particularly beneficial for drugs that have a narrow absorption window, are unstable in alkaline pH, or are primarily active in acidic conditions within the stomach [29]. For example, studies have shown the successful development of oral raft-forming in situ gelling systems for the anticancer drug **Nizatidine**, aiming to improve gastric retention and provide controlled drug release [34]. Such formulations ensure that the drug remains in the stomach for a prolonged period, maximizing its therapeutic effects in the gastrointestinal tract and improving overall treatment outcomes [34]. This prolonged and predictable drug delivery helps in maintaining a relatively constant plasma drug profile, offering advantages over conventional therapeutics for various gastrointestinal disorders like gastroesophageal reflux disorder, acid reflux, peptic ulcers, and esophagitis [27].

Enhanced Evaluation Methods

To ensure the efficacy and safety of GRDDS, robust evaluation methods are continuously being refined. Beyond the in vitro gelling, buoyancy, viscosity, and dissolution studies mentioned previously, there is an increasing focus on developing models that closely mimic the complex physiological environment of the human body [35]. This includes:

- **Biorelevant In Vitro Models:** These advanced models aim to simulate physiological conditions more accurately than traditional dissolution apparatuses, providing better predictions of in vivo performance [35,36].
- **In Vitro-In Vivo Correlation Studies:** These studies are crucial for understanding and predicting how a drug's release in an in vitro setting correlates with its absorption and bioavailability in living systems [37].
- **Ex Vivo Methods:** These techniques utilize excised animal tissues to study drug permeability and interaction with biological barriers, offering a bridge between in vitro and in vivo studies [35].
- **Advanced Imaging Techniques:** While not explicitly detailed in the recent search results for raft systems, advanced imaging (e.g., scintigraphy or MRI) in in vivo studies can track the movement and retention of GRDDS in real-time, providing critical insights into their performance.

These advanced evaluation methods are vital for the systematic design and development of GRDDS, ultimately leading to more reliable and effective therapeutic outcomes.

Applications of Raft-Forming Systems

Raft-forming systems are specifically designed to treat various gastrointestinal disorders where localized and prolonged drug action in the stomach is beneficial. These include conditions such as gastroesophageal reflux disorder, acid reflux, peptic ulcers, and esophagitis [27]. Their ability to form a physical barrier and provide sustained drug release makes them an effective approach for managing these conditions.

Gastroesophageal Reflux Disease and Acid Reflux

For conditions like GERD and acid reflux, raft-forming formulations provide a unique mechanism of action that differs from traditional antacids. Instead of simply neutralizing acid, these systems form a viscous, gelatinous mass that floats on the stomach contents [38]. This floating raft acts as a physical barrier, preventing the reflux of acidic stomach contents back into the esophagus and thereby alleviating symptoms like heartburn [38,39]. Upon contact with gastric fluids, an in-situ gel-forming biopolymer (such as sodium alginate) and gas-forming agents (like carbonates or bicarbonates) interact to create this viscous, adhesive gel layer that traps carbon dioxide, lowering its density and enhancing its buoyancy on the surface of gastric fluids without affecting gastric emptying [40]. This targeted approach makes raft systems suitable for the treatment of gastro-esophageal reflux disorders [39].

Peptic Ulcers

Raft-forming systems, particularly floating drug delivery systems which include raft systems, are gaining prominence in the treatment of peptic ulcers. Peptic ulcers are characterized by inflammation and lesions in the gastric mucosa, resulting from an imbalance between aggressive factors (e.g., acid, pepsin, *H. pylori*, NSAIDs) and defensive factors (e.g., mucus, bicarbonate) [41]. By prolonging the gastric residence time, these systems can provide sustained and localized drug delivery, which is crucial for ulcer healing and protection of the gastric mucosa [42,43]. For example, they can deliver gastroprotective drugs like Rebamipide, which has low solubility and bioavailability, by enhancing its concentration at the site of action [41]. Such systems also hold potential for treating *Helicobacter pylori* infections, a common cause of peptic ulcers, by increasing drug concentration at the bacterial colonization site within the gastric mucosa, which can improve the efficacy of current treatments [44,45]. Novel approaches, such as incorporating drug-loaded hollow mesoporous silica nanoparticles into raft-forming systems, have been developed to enhance therapeutic effects on gastric ulcers by improving drug loading, dispersibility, bio-adhesion, and sustained release [42].

Esophagitis

Esophagitis, often a consequence of chronic acid reflux, also benefits from the protective barrier and sustained drug release offered by raft-forming systems. The physical barrier created by the raft helps shield the inflamed esophageal lining from further damage by gastric acid. While direct examples of raft systems specifically for esophagitis are less common in the provided excerpts, the principle of local and prolonged drug delivery to the esophagus is an important objective in developing effective dosage forms for esophageal diseases [46]. The ability of raft systems to remain buoyant and potentially coat the esophageal entrance could contribute to symptom relief and healing in esophagitis, similar to how they prevent reflux in GERD. Furthermore, newer localized esophageal delivery systems are being explored to apply active substances directly to the esophageal mucosa for conditions like eosinophilic esophagitis, demonstrating the ongoing research into targeted esophageal treatments [47].

Table 1: Applications of Raft-Forming Systems with purpose and Examples of Drugs and Formulations

Application	Description / Purpose	Examples of Drugs / Formulations
Gastroesophageal Reflux Disease (GERD) Management	Raft forms a floating barrier that prevents acid from refluxing into the esophagus.	• Gaviscon® (sodium alginate + calcium carbonate + sodium bicarbonate) • Alginate-based suspensions with antacids
Controlled / Sustained Drug Release	Raft slows drug diffusion by remaining in stomach for extended time, improving release profile.	• Raft-forming formulations of famotidine, ranitidine, ciprofloxacin (research and marketed sustained-release systems)
Localized Action in the Stomach	Raft helps retain the drug in gastric region to act locally.	• Sucralfate-alginate rafts for gastric ulcer protection • Amoxicillin floating raft systems for H. pylori eradication

Improved Bioavailability of Drugs with Narrow Absorption Window	Raft keeps drug in stomach/proximal small intestine, enhancing absorption of drugs absorbed mainly there.	• Raft-forming systems of metformin, riboflavin, levodopa (experimental/optimized formulations)
Treatment of Helicobacter pylori Infections	Raft traps antimicrobial agents at gastric mucosa, improving eradication efficiency.	• Raft-forming amoxicillin, clarithromycin, tetracycline combinations
Pediatric and Geriatric Formulations	Easy-to-swallow liquid rafts used instead of tablets; reduced dosing frequency.	• Pediatric raft suspensions of omeprazole, magaldrate–alginate preparations
Protection of Acid-Labile Drugs	Raft shields drugs unstable in acidic pH until they reach absorption site.	• Raft systems for proton pump inhibitors (PPIs) like omeprazole or lansoprazole
Anti-emetic Therapy	Raft enhances gastric retention, prolonging antiemetic action.	• Raft-forming systems of domperidone, ondansetron
Weight Management / Satiety-Inducing Systems	Floating alginate rafts expand in stomach → promotes feeling of fullness.	• Alginate-based satiety gels (e.g., Appethyl-type alginate systems)

Evaluation Parameters for Raft-Forming Systems

The development of successful raft-forming systems relies on a thorough evaluation of their physical and chemical properties, as well as their performance in simulated gastric environments. Key evaluation parameters typically include:

***In vitro* gelling study**

This study assesses the ability of the formulation to form a cohesive gel upon contact with gastric fluid [48]. The process typically involves immersing the raft-forming system (e.g., a tablet or liquid formulation) into simulated gastric fluid at body temperature (). Researchers observe the time it takes for the formulation to hydrate, swell, and transform into a distinct, cohesive gel layer. The quality of the gel, such as its uniformity and structural integrity, is qualitatively or semi-quantitatively assessed. A well-formed, robust gel is essential for creating a stable floating barrier that can effectively entrap gases and sustain drug release.

***In vitro* buoyancy study**

This evaluation determines the floating lag time and total floating time, ensuring the system remains buoyant for the desired duration [48,49]. The system (e.g., tablet) is introduced into a dissolution vessel containing simulated gastric fluid (0.1 N HCl or similar acidic medium) maintained at . The FLT is recorded as the time taken for the dosage form to rise to the surface of the dissolution medium and float. The TFT is the total time the dosage form remains afloat. Buoyancy is a critical characteristic for raft-forming systems, as it dictates the duration of gastric retention. A short FLT and long TFT are desirable, indicating rapid activation and prolonged residence in the stomach.

Viscosity measurement

Viscosity measurement characterizes the consistency and flow properties of the formed raft [48]. After the raft has formed in a simulated gastric environment, a sample of the gel is typically extracted, and its viscosity is measured using a viscometer (e.g., Brookfield viscometer). This parameter is important because the viscosity of the gel directly influences its ability to act as a physical barrier against reflux and to control the rate of drug diffusion. A sufficiently high viscosity helps maintain the raft's integrity and prolong drug release, while an excessively high viscosity might hinder drug dissolution.

Density measurement

Density measurement confirms that the formulation's density is less than that of gastric fluid, allowing it to float [48]. The density of the formed raft is determined using methods such as liquid displacement or by calculating mass per unit volume. For a system to float effectively, its density must be less than , which is the approximate density of gastric fluid. This property is fundamental to the mechanism of floating gastroretentive systems, as it ensures the raft remains on the surface of the stomach contents rather than sinking and being rapidly emptied.

Gel strength and raft resilience

These evaluations assess the mechanical integrity and stability of the raft [48]. Gel strength can be evaluated by determining the force required to break the gel structure. Raft resilience often refers to the ability of the gel to withstand mechanical stress (e.g., from stomach contractions or agitation) without disintegrating. These tests are vital for predicting how well the raft will maintain its structure and function under the dynamic physiological conditions of the stomach. A robust and resilient raft is necessary for sustained drug delivery and for forming a stable barrier against reflux.

Drug content and acid neutralization capacity

Drug content analysis ensures the correct amount of drug is present within the formulation [48]. This is typically performed using validated analytical techniques such as high-performance liquid chromatography or UV-Vis spectrophotometry on dissolved or extracted samples of the raft. Acid neutralization capacity measures the ability of the formulation to neutralize gastric acid. This is particularly relevant for antacid components within raft systems. ANC is usually determined by titrating the raft formulation with a standard acid solution until a specific pH endpoint is reached, quantifying the amount of acid neutralized. Accurate drug content guarantees consistent dosing, while ANC confirms the therapeutic potential of acid-neutralizing raft components.

***In vitro* dissolution study**

This study measures the rate and extent of drug release from the raft under simulated gastric conditions [48,50]. Dissolution testing is commonly performed using USP dissolution apparatus (e.g., paddle or basket apparatus) with simulated gastric fluid (pH 1.2, typically 0.1 N HCl) at . Samples of the dissolution medium are withdrawn at predetermined time intervals and analyzed for drug concentration using appropriate analytical methods. The results are plotted as cumulative drug release versus time, providing a dissolution profile. This profile is crucial for understanding how the drug is released from the raft over time, which directly impacts its absorption and overall therapeutic effect. It helps confirm that the system provides the intended sustained release characteristics.

Challenges in Developing Raft-Forming Systems

Despite their potential, the development of gastroretentive drug delivery systems, including raft-forming systems, faces several challenges. These can include inter-subject variability in gastric physiology, physiological constraints that might affect performance, and issues related to manufacturing scalability [26]. For instance, the highly variable nature of gastric emptying can make it difficult to predict drug bioavailability and plasma levels [51]. Researchers continuously strive to overcome these hurdles through advancements in materials and fabrication techniques, such as 3D printing, spray drying, and nanoparticle encapsulation, to precisely modulate drug release kinetics and retention properties [52].

Furthermore, the stability of raft-forming systems, particularly regarding their gel integrity and drug release profile over extended periods, presents another significant challenge that necessitates careful excipient selection and formulation optimization. Specific attention must also be paid to the interaction between the drug and excipients, which can be evaluated through techniques like Fourier transform infrared spectroscopy and differential scanning calorimetry to ensure chemical compatibility and stability within the raft matrix.

Conclusion

This comprehensive review highlights the critical role of raft-forming systems as an advanced gastroretentive drug delivery strategy. These systems are particularly valuable for enhancing drug absorption and patient compliance, especially in the context of chronic conditions requiring sustained drug levels. The inherent advantages of raft-forming systems stem from their ability to extend gastric residence time and facilitate localized therapeutic action, making them a suitable approach for addressing various gastrointestinal disorders. Their mechanism involves the creation of a thick, cohesive gel that floats on gastric fluids due to its low density. This floating layer acts as a physical barrier against reflux and ensures the drug is released steadily over time, providing sustained drug release and acting as a physical barrier against reflux.

The development of these systems is supported by relatively straightforward in vitro and in vivo evaluation methods, coupled with the availability of suitable excipients and ease of preparation. This underscores their significant promise in pharmaceutical development, offering an effective means to improve the bioavailability and therapeutic efficacy of orally administered drugs. Despite challenges such as inter-subject variability in gastric physiology and manufacturing scalability, ongoing advancements in materials science and fabrication techniques continue to refine and optimize these innovative drug delivery systems.

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