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Review Article

Gastroretentive Floating Drug Delivery Systems of Ranitidine Hydrochloride: A Review

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ABSTRACT

Gastroretentive drug delivery systems (GRDDS) are oral dosage forms designed to prolong gastric residence time and thereby support sustained drug release, site-specific delivery, and improved exposure for suitable drug candidates. Floating drug delivery systems (FDDS) are an important GRDDS approach because a dosage form with an effective density lower than the surrounding gastric contents can remain buoyant while releasing drug in a controlled manner. Ranitidine hydrochloride has historically been investigated as a model drug for gastroretentive delivery because of its short elimination half-life, incomplete oral bioavailability, and clinically relevant absorption from the upper gastrointestinal tract. This review summarizes the physiological basis of gastric retention, major GRDDS approaches, principles of floating systems, formulation components, polymers, preparation methods, pharmacokinetic characteristics, and in vitro and in vivo evaluation methods. Effervescent and non-effervescent floating systems are discussed together with expandable, mucoadhesive, raft-forming, high-density and related approaches. The review also considers recent advances such as advanced polymer systems and three-dimensional printing, as well as the importance of fed-fasted variability, gastric motility, formulation integrity, and translational evaluation. A separate regulatory perspective is included because the historical safety issue associated with NDMA impurities led to major market withdrawal actions, while a reformulated ranitidine product was approved by the US FDA in 2025. Thus, the pharmaceutical relevance of ranitidine should be interpreted within its current regulatory context. Overall, gastroretentive floating systems remain an important formulation platform for drugs for which prolonged gastric residence can provide a meaningful biopharmaceutical advantage.

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INTRODUCTION

Oral administration remains one of the most convenient and widely accepted routes for drug delivery. Nevertheless, conventional oral dosage forms may be limited by rapid gastric emptying, variable gastrointestinal transit, incomplete absorption, short residence at the desired absorption site, and fluctuations in plasma drug concentrations. These limitations have stimulated the development of gastroretentive and controlled-release systems intended to prolong the time during which a dosage form remains in the stomach. The supplied manuscript identifies GRDDS as particularly useful for drugs that are absorbed in the stomach or upper small intestine, are unstable in the intestinal environment, have pH-dependent solubility, or possess a narrow absorption window. Examples described in the source include albuterol, ranitidine, metformin, furosemide, diazepam, riboflavin and levodopa.^{1,5}

Floating drug delivery systems are also called hydrodynamically controlled systems. Their basic design principle is to achieve a density lower than that of gastric contents so that the dosage form remains buoyant. While it floats, the system can release drug gradually and potentially delay gastric emptying while the system remains buoyant. The source manuscript notes that floating systems can be prepared as granules, powders, capsules, tablets, laminated films and hollow microspheres.¹⁶

Ranitidine hydrochloride has been used extensively as a model compound in gastroretentive formulation research. Historically, it was used as an H₂-receptor antagonist for acid-related disorders, and its relatively short half-life and need for repeated dosing provided a rationale for sustained-release investigation. The supplied draft reports oral bioavailability of approximately 50–60% and rapid absorption, with an early plasma concentration peak followed by a second peak.^{12,21}

The purpose of this review is to organize the established principles of GRDDS and FDDS, explain their relevance to ranitidine hydrochloride, summarize formulation and evaluation strategies, and incorporate recent developments that influence the design and translational assessment of gastroretentive systems.

2. REVIEW METHODOLOGY

This narrative review synthesizes literature on the physiological basis of gastric retention, classification of gastroretentive drug delivery systems, floating systems, polymers, formulation approaches, pharmacokinetic characteristics, evaluation methods, therapeutic applications, recent advances, and the current regulatory context of ranitidine. The physiological basis of gastric retention, classification of GRDDS, floating systems, polymers, formulation methods, pharmacokinetics, evaluation parameters and applications. Additional literature was consulted to update emerging technologies and recent perspectives on GRDDS.

Recent literature was identified from biomedical indexing and publisher sources using combinations of terms such as gastroretentive drug delivery system, floating drug delivery system, gastric retention, advanced polymers, three-dimensional printing and ranitidine hydrochloride. Priority was given to review articles and primary authoritative sources that directly addressed formulation principles, evaluation, recent technological development or regulatory information. The current IJPS author guidance was also checked to align the manuscript with the journal's requirements for review articles, including A4 paper size, one-inch margins, Times New Roman font, single spacing, and Vancouver-style references.²⁸

Because this is a narrative review rather than an original experimental study, no new laboratory, animal, or human experiments were performed for preparation of this manuscript. Experimental findings discussed in the review are identified as results reported in the cited literature.

Scope and organization

The review is organized from the physiological problem to the formulation solution. It first describes the stomach and factors controlling gastric residence. It then classifies gastroretentive systems and discusses floating systems in detail. The formulation section covers polymers, excipients, gas-generating agents, preparation methods and critical quality attributes. Ranitidine hydrochloride is then considered from physicochemical and pharmacokinetic perspectives. Evaluation methods, therapeutic applications, recent



advances, limitations and future directions are subsequently discussed. A specific section on the regulatory history of ranitidine is included because contemporary development decisions must account for the NDMA impurity issue and current product status.

Key review questions

- Why is gastric retention useful for selected oral drug candidates?
- What physiological and formulation factors determine gastric residence and buoyancy?
- How do effervescent and non-effervescent floating systems differ in mechanism and design?
- Which polymers and excipients are commonly used to control swelling, buoyancy and drug release?
- What pharmacokinetic characteristics historically supported gastroretentive investigation of ranitidine hydrochloride?
- Which in vitro and in vivo tests are needed to demonstrate the performance of a gastroretentive dosage form?
- What recent technologies may improve design, reproducibility and personalization of gastroretentive systems?
- How should the historical and current regulatory status of ranitidine be considered in future formulation research?

3. PHYSIOLOGICAL BASIS OF GASTRIC RETENTION

The stomach is a dynamic organ in which anatomy, motility, meal composition, fluid volume and the fed or fasted state determine the residence of an orally administered dosage form. The supplied manuscript divides the stomach into the fundus, body and antrum/pylorus. The fundus and body act mainly as a reservoir, whereas the antrum has an important role in mixing and gastric emptying. The pylorus forms the transition into the duodenum and is a major determinant of whether a dosage form can pass into the small intestine.

In the interdigestive state, gastric motility can be considered as a cyclic process. Published literature describes four phases: Phase I, a basal period with few contractions; Phase II, a period of increasing intermittent activity; Phase III, a short burst of intense and regular contractions that clears residual material; and Phase IV, a brief transition back to the next cycle.^{10,20} The strong contractions of Phase III are particularly important because they can propel retained materials toward the pylorus.

Food markedly changes gastric motility and residence time. Published literature reports that high-fat or protein-rich meals can increase gastric residence and that food quantity, caloric content and meal frequency influence the retention of floating dosage forms.¹⁶ Therefore, an apparently successful formulation in a static dissolution medium cannot automatically be assumed to exhibit identical residence in every patient or under every nutritional condition.



Factors affecting gastric retention

Factor	Influence on gastric residence	Formulation implication
Fed/fasted state	Changes motility and emptying pattern	Performance should be evaluated under physiologically relevant conditions
Meal composition	Fat, protein and caloric content can modify residence	Buoyancy should remain effective despite variable gastric contents
Dosage-form density	Low-density systems can remain buoyant	Target density should be below gastric contents during use
Dosage-form size	Large or expandable systems may resist pyloric passage	Size must balance retention with safe administration
Polymer hydration	Hydration creates a gel barrier and can support buoyancy	Polymer grade and concentration are critical
Gas generation	CO ₂ lowers effective density in effervescent systems	Gas-generating components must be uniformly distributed
Gastric motility	Strong contractions may promote emptying	Floating strength and matrix integrity must be maintained

These physiological variables explain why gastric retention is not simply a property of the tablet itself. Retention represents an interaction between dosage-form design and the dynamic gastric environment. Modern GRDDS development therefore emphasizes both formulation attributes and physiological variability.

4. GASTRORETENTIVE DRUG DELIVERY SYSTEMS: CLASSIFICATION

GRDDS can be broadly divided into floating and non-floating approaches. The supplied manuscript

discusses floating, swelling/expandable, mucoadhesive or bioadhesive, raft-forming and high-density systems, while other literature also describes magnetic and ion-exchange approaches.^{10,13,16} Recent reviews continue to consider floating, mucoadhesive, expandable, high-density, raft-forming and related systems as important gastroretentive strategies. Modern research additionally explores advanced manufacturing methods such as three-dimensional printing.^{30,32}

System	Principal mechanism	Important features	Main considerations
Floating	Buoyancy in gastric contents	Low-density matrix; effervescent or non-effervescent	Food and motility influence performance
Swelling/expandable	Increase in size after hydration	May resist pyloric passage	Safety, mechanical integrity and size are critical
Mucoadhesive	Adhesion to gastric mucosa	Uses adhesive polymers	Mucus turnover may reduce retention
Raft-forming	Formation of buoyant polymeric gel	Often combines alginate/polymer with gas-generating agents	Gel strength and gastric conditions affect performance
High-density	Density greater than gastric contents	Designed to settle in the lower stomach	Evidence for predictable long retention is variable
Magnetic	External magnetic field retains system	Can provide controlled positioning	Requires specialized materials and external control
Ion-exchange	Drug binding and exchange with ions	Can modify release and retention	Material selection and ionic environment matter

4.1 Floating systems

Floating systems are the most extensively investigated GRDDS approach because their mechanism is

conceptually simple: a dosage form remains at or near the gastric surface while releasing drug. The dosage form should generate sufficient upward force to offset its weight. Published literature notes that a density



below approximately 1 g/mL is commonly associated with buoyancy, although bulk density alone does not fully describe floating performance. Resultant weight, floating force and swelling behavior can provide more informative measures.

4.2 Non-floating gastroretentive systems

Non-floating systems use other mechanisms to resist gastric emptying. Swelling systems absorb gastric fluid and increase their dimensions; mucoadhesive systems attempt to maintain contact with gastric mucosa; raft-forming systems create a cohesive buoyant gel; and high-density systems are designed to remain in the lower region of the stomach. Each approach introduces its own formulation and translational challenges, and no single mechanism is universally appropriate for all drug candidates.

5. FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery systems can be categorized into effervescent and non-effervescent systems. Effervescent systems use gas-generating materials, commonly carbonates or bicarbonates with an acid source, to generate carbon dioxide after contact with gastric fluid. The resulting gas becomes entrapped within the hydrated matrix and lowers the effective density. Non-effervescent systems instead depend mainly on polymer hydration, swelling, gel formation and the entrapment of air within a low-density matrix.

5.1 Effervescent systems

Gas-generating floating tablets generally contain the drug, a hydrophilic matrix polymer and a gas-generating component. Sodium bicarbonate is commonly used, sometimes with an organic acid such as citric acid. Upon contact with acidic gastric fluid, carbon dioxide is produced. The rate and extent of gas generation depend on the amount and distribution of the gas-generating materials, matrix permeability and the availability of gastric fluid.

Single-layer hydrodynamically balanced systems combine drug and matrix components in one unit. Bi-layer systems can separate immediate-release and sustained-release functions, allowing an initial dose to be followed by prolonged release. The supplied manuscript also describes volatile-liquid or vacuum-

containing systems, in which a floating compartment is created using air, gas or a volatile liquid. These systems are technically more complex than ordinary matrix tablets.

5.2 Non-effervescent systems

Non-effervescent systems generally rely on gel-forming polymers such as HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose and sodium carboxymethyl cellulose. After exposure to gastric fluid, the polymer hydrates and develops a gel barrier. The hydrated matrix controls fluid penetration and drug diffusion. Entrapped air and matrix swelling can contribute to buoyancy. This approach avoids reliance on an acid-base gas-generating reaction but places greater importance on polymer grade, viscosity, concentration, matrix integrity and hydration kinetics.

5.3 Major non-effervescent designs

- Hydrodynamically balanced/colloidal gel barrier systems: hydrophilic polymers hydrate and form a floating gel matrix.
- Microporous compartment systems: a drug reservoir is protected within a compartment that permits controlled interaction with gastric fluid.
- Alginate beads: porous calcium alginate structures can remain buoyant for prolonged periods under suitable conditions.
- Microballoons or hollow microspheres: internal voids reduce density and support prolonged buoyancy.
- Expandable systems: the dosage form enlarges after hydration and may resist passage through the pylorus.
- Mucoadhesive systems: polymers interact with the gastric mucosa to prolong contact.
- Raft-forming systems: a cohesive polymeric gel forms at the gastric surface and may provide short-term retention.

6. POLYMERS AND EXCIPIENTS USED IN GRDDS

Polymers determine many of the critical performance characteristics of gastroretentive systems, including



hydration, swelling, gel strength, drug diffusion, matrix erosion and mechanical integrity. The supplied manuscript divides polymers into natural and synthetic categories. Natural materials include chitosan, pectin, xanthan gum, guar gum, alginate, gellan gum, starch, karaya gum, tamarind gum, aloe mucilage, psyllium

husk, tara gum, okra gum, carrageenan and arabino-galactan. Synthetic or semisynthetic materials include HPMC grades, carbopol, ethyl cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinyl alcohol, hydroxypropyl cellulose, hydroxyethyl cellulose, Eudragit grades and PVP.

Polymer/material	Category	Typical role in GRDDS
HPMC K4M/K15M/K100M	Hydrophilic polymer	Gel formation, swelling and sustained release
Hydroxyethyl cellulose	Hydrophilic polymer	Matrix formation and controlled release
Hydroxypropyl cellulose	Hydrophilic polymer	Hydration and release control
Sodium CMC	Hydrophilic polymer	Gel formation and viscosity modification
Carbopol 934P	Polyacrylic acid polymer	Matrix integrity and release retardation
Alginate	Natural polysaccharide	Gel formation and raft/floating systems
Chitosan	Natural polysaccharide	Mucoadhesion and matrix formation
Xanthan gum	Natural polysaccharide	Viscosity, swelling and sustained release
Ethyl cellulose	Hydrophobic polymer	Release retardation and buoyancy support
PVP	Synthetic polymer	Binder/film-forming and formulation support

6.1 Selection criteria

Polymer selection should consider viscosity grade, hydration rate, swelling capacity, compatibility with the drug, mechanical strength, release kinetics and the intended manufacturing process. High-viscosity polymers can form stronger gel barriers but may slow release excessively. Lower-viscosity grades may hydrate rapidly but provide less mechanical integrity. Combining polymers can therefore provide a useful balance between buoyancy, strength and drug release.

6.2 Gas-generating and supporting excipients

Sodium bicarbonate is a common gas-generating agent, while citric acid or another acid source can facilitate carbon dioxide generation. Lactose and mannitol may act as release-rate accelerants or fillers, whereas dicalcium phosphate, talc and magnesium stearate can retard release or assist manufacturing depending on their concentration and function. Inert fatty materials such as beeswax, fatty acids, long-chain alcohols and glycerides may lower hydrophilicity and support buoyancy. Preservatives, stabilizers and lubricants can be included when appropriate.

Recent literature emphasizes that polymer selection is moving beyond conventional excipients toward advanced and modified polymers. A 2024 review highlighted alginates, chitosan, pectin, carrageenan, xanthan gum, hydroxypropyl cellulose, carbomer, polyethylene oxide and sodium carboxymethyl cellulose among important materials investigated for advanced gastroretentive systems.³⁰

7. FORMULATION DESIGN AND MANUFACTURING OF FLOATING TABLETS

Floating tablet formulation is a multivariable design problem in which buoyancy and drug release must be balanced. A formulation that floats rapidly but releases the drug too quickly does not provide sustained delivery, while a matrix that releases extremely slowly may reduce therapeutic usefulness. The formulation must also maintain adequate mechanical strength, content uniformity and stability during storage.

7.1 Wet granulation approach

The supplied manuscript describes a wet granulation method using ranitidine hydrochloride, lactose, HPMC K4MCR, sodium bicarbonate and magnesium stearate.



Components are accurately weighed and mixed, followed by wet granulation using 95% ethanol. The wet mass is dried overnight at approximately 40°C and passed through a 40-mesh screen. Dried granules may be further sieved and lubricated with magnesium stearate before compression. The original draft reports a tablet hardness range of 6.2–6.9 kg/cm² for the described formulation.

7.2 Direct compression and dry granulation

Direct compression can reduce processing steps when powder flow, compressibility and blend uniformity are

adequate. The source manuscript describes direct mixing of ranitidine hydrochloride with HPMC K4M, sodium CMC, Carbopol 934P, sodium bicarbonate and lactose followed by lubrication. Dry granulation or slugging may also be considered when the powder blend requires improved flow or compressibility without exposure to a granulating liquid.

7.3 Critical formulation variables

Variable	Effect on performance	Potential risk if excessive/insufficient
Polymer concentration	Controls gel strength and release	Too high: incomplete release; too low: rapid release
Polymer viscosity grade	Influences hydration and matrix strength	Poor balance may alter floating and release
Sodium bicarbonate	Generates CO ₂ and reduces density	Excess gas may weaken matrix or cause rapid erosion
Acid source	Controls gas-generation kinetics	Imbalance can reduce buoyancy consistency
Tablet hardness	Affects porosity and matrix integrity	Very high hardness can delay hydration
Porosity	Influences fluid penetration and gas entrapment	Too low may delay buoyancy; too high may cause rapid release
Lubricant level	Improves manufacturing	Excess may reduce wettability and affect release

7.4 Quality-by-design perspective

A systematic development strategy should identify critical material attributes and critical process parameters that affect critical quality attributes such as floating lag time, total floating duration, drug release, hardness, friability and content uniformity. Recent advances in manufacturing, including three-dimensional printing, provide additional opportunities to control internal geometry, porosity and drug-release pathways.^{31, 32}

8. RANITIDINE HYDROCHLORIDE: PHYSICOCHEMICAL AND BIOPHARMACEUTICAL PROFILE

Ranitidine hydrochloride is the hydrochloride salt of ranitidine, an H₂-receptor antagonist that historically was used for acid-related gastrointestinal disorders. The supplied manuscript identifies the compound by its systematic chemical name and reports pK_a values around 8.2 and 2.7. The draft also reports a logD value of approximately 0.24 for the ionized form and a

calculated logP of approximately 1.28 for the neutral molecule.

8.1 Solubility

The supplied draft reports high aqueous solubility for ranitidine hydrochloride, with values above 550 mg/mL over a pH range of 1–7.4 and a reported value of about 660 mg/mL in water. Based on the dose-to-solubility ratio described in the source, the drug was characterized as highly soluble.^{14, 22} These values are important because they indicate that a gastroretentive formulation of ranitidine is more likely to depend on controlled release and retention than on improving dissolution of the drug itself.

8.2 Historical therapeutic rationale for gastroretention

The source manuscript describes ranitidine as a drug requiring repeated dosing in historical clinical use, with short biological half-life and incomplete oral



bioavailability. A gastroretentive sustained-release dosage form was therefore investigated as a means of prolonging drug release and reducing fluctuations in drug exposure. This rationale is formulation-oriented

and should not be interpreted as a recommendation for current clinical treatment.

8.3 Physicochemical summary

Property	Information reported in the supplied review
Drug class	Histamine H ₂ -receptor antagonist
Dosage form studied	Gastroretentive floating tablets/capsules
Salt form	Ranitidine hydrochloride
Reported pK _a	Approximately 8.2 and 2.7
Reported logD	Approximately 0.24 for ionized form
Calculated logP	Approximately 1.28 for neutral molecule
Reported aqueous solubility	About 660 mg/mL; >550 mg/mL over pH 1–7.4 in the cited draft
Historical oral bioavailability	Approximately 50–60%
Historical elimination half-life	Approximately 1.7–2.1 h after IV dosing in cited source
Protein binding	Approximately 15%

These physicochemical characteristics support the use of ranitidine hydrochloride as a model compound for studying controlled gastroretentive delivery, particularly when the research objective is to examine prolonged release and gastric retention rather than solubility enhancement.

9. PHARMACOKINETIC CHARACTERISTICS

9.1 Absorption

The supplied manuscript reports oral bioavailability of approximately 50–60% and rapid oral absorption. It describes a first plasma concentration peak within approximately 0.5–1.5 hours and a second peak at about 3–4 hours. The source notes that the double-peak phenomenon is not satisfactorily explained by biliary excretion or gastric emptying and reports similar behavior when the drug is administered directly to the jejunum.^{12, 21}

Site-specific intestinal investigations have historically been used to characterize ranitidine absorption. The source review describes evidence supporting absorption primarily in the small intestine and notes lower bioavailability when the drug is delivered directly to the colon. These observations provided a scientific

rationale for exploring dosage forms that maintain the drug in the upper gastrointestinal region for an extended period.

9.2 Distribution

The supplied draft reports an apparent terminal volume of distribution of approximately 1.16–1.87 L/kg and low protein binding of approximately 15%. These properties indicate relatively limited plasma protein binding and a distribution profile that is relevant to pharmacokinetic interpretation of sustained-release dosage forms.

9.3 Metabolism and excretion

Ranitidine is substantially eliminated through the kidneys. The source manuscript reports urinary excretion of unchanged drug after intravenous administration at approximately 70–80%, with about 25–30% of the orally administered dose excreted unchanged in urine. It reports that less than 10% of the dose is metabolized and excreted in urine and that approximately 26% of orally administered drug is excreted in feces. The cited elimination half-life after intravenous administration is approximately 1.7–2.1 hours.^{4, 6}

Parameter	Reported value in supplied review	Formulation relevance
Oral bioavailability	50–60%	Suggests potential value of optimized exposure
First plasma peak	0.5–1.5 h	Indicates rapid absorption
Second peak	3–4 h	Supports complex absorption behavior



Parameter	Reported value in supplied review	Formulation relevance
Protein binding	~15%	Low binding
Apparent terminal Vd	1.16–1.87 L/kg	Distribution characteristic
Renal excretion	Substantial	Renal clearance is important
IV elimination half-life	1.7–2.1 h	Short duration supports controlled-release rationale

9.4 Implications for floating delivery

From a formulation perspective, the historical pharmacokinetic profile creates a clear design target: maintain a consistent release rate over an extended period without producing dose dumping or excessive delay in absorption. However, the success of a gastroretentive system cannot be judged only from an in vitro dissolution curve. Gastric residence, fed-fasted state, intestinal permeability, renal function and formulation integrity all influence systemic exposure. In vivo pharmacokinetic studies are therefore important when translating promising floating formulations.

10. EVALUATION OF GASTRORETENTIVE FLOATING SYSTEMS

Evaluation of GRDDS should demonstrate that the dosage form has acceptable pharmaceutical quality and that its gastroretentive mechanism functions as

intended. The supplied manuscript separates in vitro and in vivo evaluation. Important in vitro tests include tablet dimensions, hardness/tensile strength, weight variation, friability, drug content, content uniformity, dissolution, floating lag time, total floating duration, floating force, swelling and water uptake.²⁵

10.1 Pre-compression evaluation

- Angle of repose and flow properties of powder/granules.
- Bulk and tapped density.
- Compressibility index and Hausner ratio.
- Moisture content where relevant.
- Blend uniformity and drug-excipient compatibility.

10.2 Post-compression evaluation

Test	Purpose	Typical interpretation
Appearance	Visual quality and integrity	Uniform, defect-free tablets
Weight variation	Dose-unit consistency	Within applicable pharmacopoeial limits
Hardness/tensile strength	Mechanical integrity	Adequate strength without excessive resistance to hydration
Friability	Resistance to abrasion	Low mass loss
Drug content	Assay of active ingredient	Within specified limits
Content uniformity	Unit-to-unit dose consistency	Acceptable variability
Floating lag time	Time to achieve buoyancy	Short and reproducible
Total floating time	Duration of buoyancy	Sufficient for intended release period
Floating force	Quantitative buoyancy measurement	Adequate upward force
Swelling index	Hydration and matrix expansion	Controlled, reproducible swelling
In vitro dissolution	Drug-release profile	Controlled and reproducible release

10.3 In vitro floating evaluation

Floating lag time is measured from immersion until the dosage form reaches the surface and remains buoyant. Total floating duration measures how long the system remains afloat. Floating force provides a more quantitative assessment of buoyancy than visual observation

alone. Dissolution studies should use a suitable gastric or simulated gastric medium and should continue long enough to capture both buoyancy behavior and the intended release phase. The supplied review recommends extended testing, with at least eight hours used in the described evaluation context.



10.4 In vivo evaluation

In vivo assessment can use imaging techniques to track dosage-form location and residence. Gamma scintigraphy can track radiolabeled dosage forms, X-ray can use radio-opaque markers, gastroscopy can directly visualize the stomach, ultrasonography can assess location, and magnetic resonance imaging can provide non-invasive imaging when appropriate contrast materials are available.^{11,13} These methods are valuable because in vitro buoyancy does not directly prove gastric retention in humans.

11. APPLICATIONS AND THERAPEUTIC RELEVANCE

Floating systems are most rational for drugs whose therapeutic performance may benefit from prolonged gastric residence. Examples include drugs intended for local gastric action, drugs with a narrow upper gastrointestinal absorption window, drugs that require prolonged exposure to acidic conditions, and drugs for which sustained release can reduce dosing frequency.

11.1 Sustained drug delivery

Hydrophilic buoyant matrices can maintain a dosage form in the stomach while releasing drug over several hours. The supplied manuscript describes examples involving nicardipine hydrochloride and other model drugs in which floating formulations extended drug release compared with conventional products. Such examples illustrate the general principle that gastric retention can be combined with matrix-controlled release.

11.2 Site-specific delivery

Drugs absorbed preferentially from the stomach or proximal small intestine may benefit from prolonged residence near the absorption region. The supplied review cites furosemide and riboflavin as examples of drugs for which upper gastrointestinal delivery has been investigated. It also reports increased AUC with a monolithic floating furosemide dosage form compared with conventional treatment in the cited study.

11.3 Absorption enhancement

By maintaining a dosage form in the upper gastrointestinal tract, floating systems can increase the

opportunity for drug dissolution and absorption when the relevant absorption window is limited. The effect, however, is drug-specific and should be demonstrated experimentally rather than assumed from buoyancy alone.

11.4 Potential relevance to ranitidine hydrochloride

Historically, ranitidine hydrochloride provided a useful model for studying gastroretentive sustained release because of its short half-life, repeated-dosing requirements and upper gastrointestinal absorption characteristics. Floating tablets and capsules could therefore be designed to provide prolonged release while attempting to maintain the dosage form in the stomach. The therapeutic rationale is historical and formulation-focused; current clinical use must be considered separately in light of regulatory developments discussed later in this review.

11.5 Advantages

- Potential improvement in drug exposure for suitable absorption-window drugs.
- Prolonged and controlled drug release.
- Potential reduction in dosing frequency.
- Reduced peak-to-trough fluctuations when release is appropriately controlled.
- Possibility of site-specific delivery in the stomach or upper intestine.
- Useful platform for studying drug-polymer and buoyancy-release relationships.

11.6 Limitations

- Variable gastric emptying between individuals.
- Strong migrating motor complex contractions can promote gastric emptying.
- Food and meal composition alter residence.
- Some drugs are unsuitable for prolonged gastric exposure.
- Buoyancy does not guarantee prolonged in vivo retention.
- Complex formulations may be difficult to manufacture reproducibly.



- Safety and tolerability must be established for expandable or highly adhesive systems.

12. RECENT ADVANCES IN GASTRORETENTIVE DELIVERY

GRDDS research has expanded beyond conventional matrix tablets toward advanced polymers, multifunctional systems and digitally controlled manufacturing. Recent reviews emphasize that the field is increasingly focused on overcoming the variability of gastric physiology and improving reproducibility, personalization and clinical translation.

12.1 Advanced polymer systems

A 2024 comprehensive review highlighted the continued development of natural and synthetic polymers for gastroretentive delivery, including alginate, chitosan, pectin, carrageenan, xanthan gum, hydroxypropyl cellulose, carbomer, polyethylene oxide and sodium carboxymethyl cellulose.³⁰ Polymer modification can alter hydration, mechanical strength, mucoadhesion and release characteristics, allowing formulation scientists to tune the balance between retention and release.

12.2 Three-dimensional printing

Three-dimensional printing is an emerging manufacturing strategy for gastroretentive dosage forms. A 2024 systematic review described 3D-printed floating systems and emphasized the ability of additive manufacturing to create complex geometries and personalized drug-delivery designs.³¹ Other recent work has reviewed 3D printing as a manufacturing approach for floating, expandable and mucoadhesive gastroretentive systems.³²

Potential advantages include control of internal voids, shell thickness, infill density, drug distribution and release pathways. These features may allow a formulation to be designed around a target floating period or release profile rather than relying solely on conventional compression variables. However, scale-up, printing reproducibility, material selection, regulatory control and process validation remain important barriers.

12.3 Natural polymer and biopolymer systems

Natural polysaccharides continue to attract attention because they can provide hydration, gel formation, swelling and, in selected cases, mucoadhesion. Recent research on xanthan-gum-based gastroretentive systems has examined chemical modification and formulation strategies intended to overcome limitations of the native polymer.³³

12.4 Data-driven formulation development

Future development is likely to combine formulation science with design-of-experiments approaches, process analytical technology and predictive modeling. Such approaches can help relate polymer concentration, viscosity, gas generation, tablet hardness and porosity to measurable critical quality attributes. The goal is to reduce trial-and-error development and improve scale-up consistency.

12.5 Clinical translation

Recent literature also emphasizes that many gastroretentive concepts show promising laboratory behavior but face translational difficulties. Variability in gastric physiology, uncertainty in long-term retention, device safety, patient acceptability and manufacturing complexity can limit clinical adoption. Thus, future research should combine robust in vitro characterization with appropriately designed in vivo and, where justified, clinical studies.

13. CURRENT REGULATORY CONTEXT OF RANITIDINE

Any contemporary review focused on ranitidine hydrochloride should distinguish its historical formulation-development literature from its current regulatory context. In 2020, the US Food and Drug Administration (FDA) requested withdrawal of all prescription and over-the-counter ranitidine products from the US market because testing showed that NDMA (N-nitrosodimethylamine) levels in some ranitidine products could increase with time and temperature.³⁴

The regulatory situation subsequently changed in the United States. On November 24, 2025, the FDA announced approval of reformulated ranitidine tablets following a comprehensive safety review and



manufacturing changes intended to address the previous NDMA impurity-formation concern. The FDA also specified storage and handling conditions for the newly approved product.³⁵

This development does not invalidate the historical gastroretentive literature, but it does change how a current review should frame ranitidine. Formulation research should not assume that older ranitidine products and newly reformulated products have identical impurity profiles, manufacturing controls or regulatory status. Any future development work should use a clearly characterized active ingredient and comply with the regulatory requirements applicable to the jurisdiction in which the product is being developed.

13.1 Implications for gastroretentive research

- Ranitidine remains a historically important model drug for gastroretentive formulation research.
- Published pre-2020 formulation studies should be interpreted in their original regulatory context.19 Oct 2026
- Current formulation studies should include appropriate impurity and stability considerations where applicable.
- Drug substance and finished-product specifications should be clearly documented.
- Claims of clinical usefulness should not be inferred solely from successful floating or dissolution behavior.
- Regulatory status differs by jurisdiction and should be verified at the time of development or submission.

13.2 Safety and stability considerations

The ranitidine NDMA experience demonstrates that chemical stability can become a major product-quality issue even when the formulation performs well from a drug-release perspective. Gastroretentive development should therefore consider not only buoyancy and dissolution but also chemical stability, degradation pathways, packaging, storage temperature and the potential formation of process- or storage-related impurities.

14. CRITICAL DISCUSSION AND FUTURE PERSPECTIVES

Floating gastroretentive systems remain attractive because the design principle is relatively straightforward and can be implemented using conventional pharmaceutical excipients and manufacturing technologies. However, the major challenge is that the stomach is not a static dissolution vessel. Gastric motility, food, fluid volume, pyloric opening, patient variability and disease state can all affect the residence of a dosage form.

14.1 From buoyancy to verified gastric retention

A major conceptual distinction is the difference between in vitro floating and actual in vivo gastric retention. A tablet can remain buoyant for many hours in simulated gastric fluid yet leave the stomach earlier than expected in a human subject. Consequently, floating lag time and total floating duration should be regarded as formulation characteristics, whereas gastric residence time is an in vivo physiological outcome. Imaging and pharmacokinetic studies provide stronger evidence of clinical relevance.

14.2 Balancing retention and release

The optimal formulation is not necessarily the formulation with the longest floating time. Excessively prolonged retention without appropriate drug release may provide little benefit. Similarly, rapid release from a floating dosage form may fail to provide the intended sustained-delivery advantage. Development should therefore target a coordinated profile in which buoyancy, swelling, matrix integrity and dissolution remain synchronized.

14.3 Patient variability

Future gastroretentive systems should be designed with fed-fasted variability in mind. A formulation that depends on a particular gastric volume or meal condition may have inconsistent performance across patients. Multi-unit systems, robust low-density matrices and adaptable polymer architectures may help reduce some sources of variability, but these solutions require direct experimental validation.



14.4 Future research directions

- Development of robust polymers with predictable hydration and mechanical properties.
- Use of multi-unit floating systems to reduce the effect of individual-unit variability.
- Advanced manufacturing, including 3D printing, for controlled geometry and personalized dosing.
- Integration of imaging, dissolution and pharmacokinetic measurements to establish in vitro–in vivo relationships.
- Use of quality-by-design and design-of-experiments approaches for systematic optimization.
- Improved prediction of fed-fasted gastric behavior using biorelevant testing.
- Greater attention to chemical stability and impurity control during gastroretentive formulation development.
- Evaluation of patient acceptability and real-world dosing behavior before clinical translation.

14.5 Overall perspective

Published evidence supports GRDDS as a formulation strategy for selected drug candidates, but successful development requires a drug-specific and physiology-aware approach. Floating systems are particularly attractive when the drug benefits from prolonged residence in the upper gastrointestinal tract. For ranitidine hydrochloride, historical pharmacokinetic characteristics provided a rationale for formulation research, while the current regulatory environment requires careful consideration of product identity, stability and impurity control. 19 Oct 2026

CONCLUSION

Gastroretentive drug delivery systems provide a formulation strategy for prolonging gastric residence and controlling oral drug release. Floating drug delivery systems remain one of the most extensively investigated approaches because their low-density dosage forms can remain buoyant in gastric contents while releasing drug in a controlled manner. The performance of these systems depends on a combination of formulation factors, including polymer type and

concentration, matrix hydration, gas generation, tablet density, porosity, mechanical strength and release kinetics.

Ranitidine hydrochloride has historically been an important model drug for gastroretentive formulation because of its short half-life, repeated-dosing requirements and upper gastrointestinal absorption characteristics. Published literature describes multiple floating formulations using hydrophilic polymers such as HPMC, Carbopol and sodium carboxymethyl cellulose, together with gas-generating agents such as sodium bicarbonate. Evaluation requires a combination of pharmaceutical quality tests, floating behavior, dissolution, swelling and, when appropriate, in vivo gastric-retention and pharmacokinetic assessment.

Recent developments in advanced polymers, natural biopolymers, multi-unit systems and three-dimensional printing indicate that gastroretentive delivery continues to evolve. At the same time, physiological variability and the gap between in vitro buoyancy and in vivo retention remain important barriers to translation. For ranitidine specifically, the historical NDMA-related regulatory withdrawal and the subsequent 2025 US FDA approval of a reformulated product demonstrate why current development must incorporate contemporary quality, stability and regulatory considerations.

Overall, the future of gastroretentive delivery will depend on rational drug selection, robust formulation design, physiologically relevant evaluation and evidence that the proposed retention mechanism provides a measurable biopharmaceutical or therapeutic advantage.

DECLARATION

Conflict of Interest

The authors declare that there are no known financial or personal conflicts of interest related to this review.

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