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Floating Microspheres for Sustained Oral Drug Delivery: Formulation Strategies, Ionic Gelation Techniques, and In Vitro Evaluation

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Abstract

Floating microspheres have emerged as an effective gastroretentive multiparticulate system for sustained oral drug delivery, particularly for drugs that require prolonged gastric residence or controlled release in the upper gastrointestinal tract. By maintaining a density lower than gastric fluid, floating microspheres remain buoyant in the stomach, thereby reducing premature gastric emptying and improving drug availability. Among the various fabrication approaches, the ionic gelation technique has gained significant attention due to its simplicity, mild processing conditions, and suitability for biocompatible and biodegradable polymers. In this technique, polymeric solutions containing the drug undergo ionic crosslinking in the presence of multivalent ions, leading to the formation of discrete, low-density microspheres with controlled structural and release properties. The performance of ionic gelation—based floating microspheres is strongly influenced by formulation variables such as polymer type and concentration, crosslinking agent, and processing parameters, which collectively govern buoyancy, drug entrapment, swelling behavior, and release kinetics. In vitro evaluation plays a crucial role in characterizing these systems and typically includes assessment of micromeritic properties, floating behavior, swelling index, surface morphology, and drug release profiles. This review critically discusses formulation strategies, the ionic gelation method, key influencing factors, and standard in vitro evaluation techniques, while also highlighting current challenges and future perspectives in the development of floating microspheres for sustained oral drug delivery.

Keywords

Floating microspheres; gastroretentive drug delivery; sustained oral delivery; ionic gelation; polymeric microspheres; buoyancy; in vitro characterization; controlled release; release kinetics.

1. Introduction

Oral drug delivery remained the most convenient and commonly preferred route in clinical practice because it generally enabled self-administration, supported flexible dosing, and reduced the need for invasive procedures. Despite these advantages, conventional immediate-release oral dosage forms often showed limitations that translated into suboptimal therapeutic outcomes, particularly when a drug exhibited a short biological half-life, narrow absorption window, instability in the distal intestine, or a need for sustained plasma concentrations. In such cases, frequent dosing could be required, which increased the risk of poor adherence and fluctuating drug levels. These constraints motivated continued development of controlled-release strategies that could extend drug input, reduce dosing frequency, and improve patient compliance while maintaining safety.

Gastroretentive drug delivery systems were developed to address one of the most consequential physiological barriers to sustained oral performance, namely the variable and often short gastric residence time of conventional dosage forms. Gastric emptying was influenced by complex factors that included the fed or fasted state, meal composition and caloric density, circadian rhythm, posture, inter-individual variability, and disease status affecting motility. When a formulation emptied rapidly from the stomach, drugs that were primarily absorbed in the stomach or proximal small intestine could show incomplete absorption and reduced bioavailability. Additionally, drugs intended for local action in the stomach, or drugs that

benefited from prolonged exposure to acidic pH for dissolution or controlled release, could exhibit reduced effectiveness if gastric residence was insufficient.

Among gastroretentive strategies, floating drug delivery systems were extensively studied because buoyancy could be used to keep a dosage form in the gastric region for longer periods, potentially improving both residence time and the consistency of drug delivery. Floating systems were broadly conceptualized to maintain a lower density than gastric fluid, allowing them to remain at or near the top of the gastric contents. While floating tablets and capsules offered practical manufacturing routes, they could also demonstrate variability, particularly when gastric motility was strong or when a single unit was prone to premature emptying. Multiparticulate approaches were therefore explored to reduce variability by distributing multiple units throughout the stomach, thereby decreasing the probability that the entire dose would be emptied at once.

Floating microspheres represented a prominent multiparticulate approach in this domain. These systems were typically designed as low-density particles, frequently with a hollow or porous internal structure, enabling prolonged buoyancy in gastric fluid while releasing drug in a sustained manner. Their multi-unit nature could reduce inter- and intra-patient variability, minimize the risk of dose dumping, and potentially improve safety profiles for drugs where high peak concentrations were undesirable. Floating microspheres also offered formulation flexibility, as polymer selection and processing conditions could be tuned to control size, density, drug loading, and release kinetics.

Within the available manufacturing techniques, ionic gelation gained particular relevance for polymeric microsphere formation because it relied on ionic crosslinking rather than harsh organic solvents or high-temperature processing. In this method, polymer chains bearing ionizable groups formed a three-dimensional network upon exposure to counter-ions, resulting in rapid gelation and microsphere formation. Ionic gelation was frequently paired with natural polymers such as alginate, often used alone or in blends with other polymers to optimize buoyancy, mechanical strength, and controlled release behaviour. The performance of these systems was commonly established through in vitro characterization, including buoyancy testing, drug entrapment analysis, swelling studies, morphological assessment, and dissolution testing under simulated gastric conditions, followed by kinetic modelling to interpret release mechanisms.

This review was structured to provide a consolidated and formulation-oriented understanding of floating microspheres prepared by ionic gelation, emphasizing the scientific basis of buoyancy, polymer-network design, key processing variables, and in vitro evaluation approaches. It further aimed to identify limitations that constrained translation and to outline research directions that could improve robustness, predictability, and scalability.

Gastroretentive Drug Delivery via Floating Microspheres

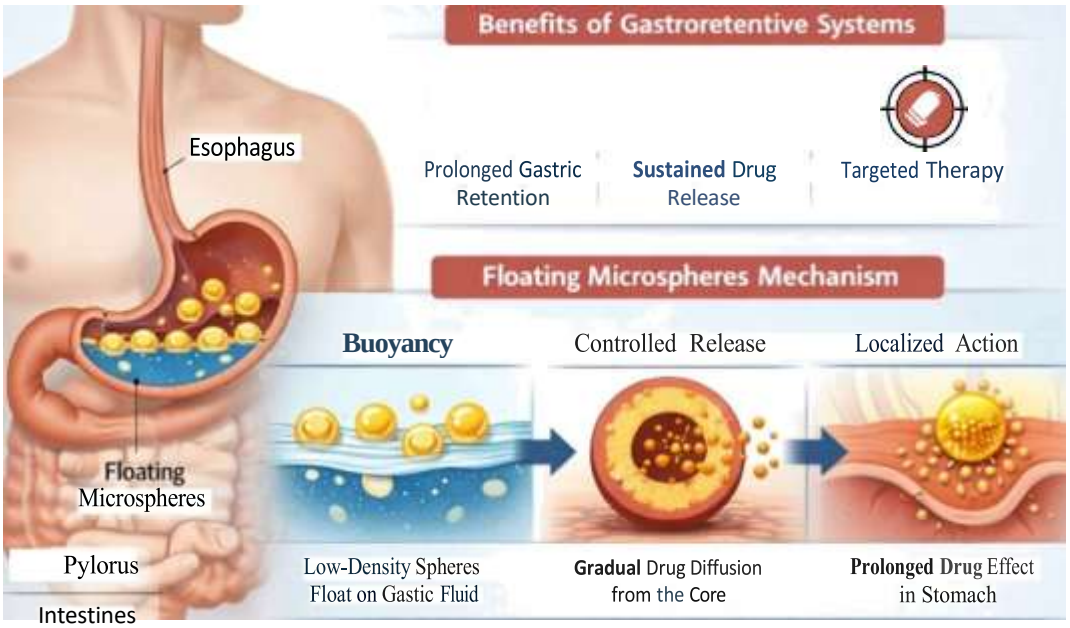


Figure 1. Conceptual schematic illustrating gastroretention by floating microspheres in the stomach,

showing buoyancy-driven retention, multiparticulate distribution, polymer hydration, and sustained drug diffusion/erosion-based release.

Table 1. Comparative overview of gastroretentive drug delivery systems

Gastroretentive approach	**Principle of retention**	**Typical materials used**	Key **advantages**	**Major limitations**
Floating drug delivery systems	Dosage form maintains density lower than gastric fluid and floats on stomach contents	Hydrophilic polymers (alginate, HPMC, chitosan), gas-generating agents (for effervescent systems)	Prolonged gastric residence; non-invasive; suitable for sustained release	Performance affected by gastric motility and fed/fasted state
Bioadhesive systems	Adhesion of dosage form to gastric mucosa	Chitosan, carbopol, polycarbophil	Increased residence time via mucosal attachment	Possible mucosal irritation; adhesion may be reduced by mucus turnover
Swelling/expandable systems	Dosage form swells to a size larger than pyloric opening	Hydrophilic swellable polymers	Effective mechanical retention	Risk of gastric obstruction; complex formulation design

High-density systems	Dosage form sinks to the bottom of the stomach	Dense excipients (e.g., barium sulfate, zinc oxide)	Reduced dependence on buoyancy	Limited clinical applicability; inconsistent retention
Floating microspheres (multiparticulate)	Multiple low-density units float and distribute throughout stomach	Alginate, chitosan, pectin, polymer blends	Reduced dose dumping; uniform distribution; better reproducibility	Formulation complexity; scale-up challenges

Table 2. Polymers commonly used in ionic gelation—based floating microspheres

Polymer	**Polymer type**	**Functional groups involved in gelation**	**Typical crosslinking ions**	**Role in floating microspheres**
Sodium alginate	Natural polysaccharide	Carboxylate groups	Calcium^{2+}, zinc^{2+}, barium“	Primary gelling agent; matrix formation; sustained release

Chitosan	Natural cationic polysaccharide	Amino groups	Tripolyphosphate, alginate (polyelectrolyte complex)	Improves mechanical strength; modulates release; mucoadhesion

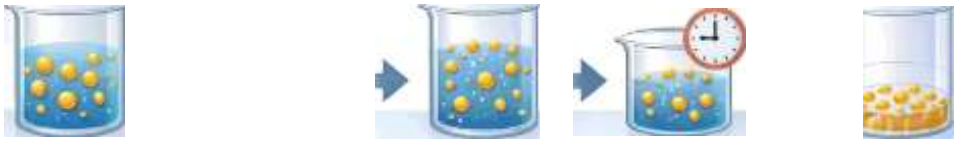
Pectin	Natural polysaccharide	Carboxyl groups	Calcium²⁺	Enhances gel strength; release modulation
Guar gum	Natural galactomannan	Hydroxyl groups (non-ionic)	— (used as secondary polymer)	Increases viscosity; reduces density; prolongs floating
Xanthan gum	Natural polysaccharide	Carboxyl and hydroxyl groups	(supporting polymer)	Swelling control; sustained release
Cellulose derivatives (e.g., HPMC)	Semi-synthetic polymer	Hydroxyl groups	— (non-crosslinked)	Controls hydration rate; reduces burst release

Table 3. In vitro evaluation parameters for floating microspheres

Evaluation parameter	**Purpose**	**Typical test conditions**	**Significance**
Particle size distribution	Determines dispersion and buoyancy	Optical microscopy / sieve analysis	Influences gastric distribution and release rate
Bulk and tapped density	Assesses packing and flow behavior	Standard pharmacopeial methods	Related to buoyancy and handling
Drug loading	Quantifies drug content in microspheres	Extraction followed by assay	Ensures dose uniformity

Entrapment efficiency	Measures encapsulation effectiveness	Drug content vs. theoretical content	Indicates formulation efficiency
Floating lag time	Time required to initiate floatation	Simulated gastric fluid, mild agitation	Indicator of immediate buoyancy
Total floating duration	Duration microspheres remain buoyant	Simulated gastric fluid	Reflects gastroretentive potential
Swelling index	Evaluates polymer hydration	Weight gain over time	Influences release and structural integrity
Surface morphology	Examines shape and porosity	Scanning electron microscopy	Correlates with buoyancy and release
In vitro drug release	Determines release profile	Dissolution apparatus, acidic media	Predicts sustained-release performance
Release kinetics modeling	Elucidates release mechanism	Mathematical model fitting	Supports mechanism-based interpretation

Ionic Gelation Technique WorkflOW for Floating Microsphere Preparation



Drug and Polymer Solution | **Droplet Formation** | **Ionic Crosslinking** | Curing | **Washing**

Drug Dispesed in Solution | Solution transferred Dropwise | Droplets Ensounter Crosslinking ions | Microspheres Allowed to cure | Excess ions & Drug Washed Away | Aqueous Polymer

5. Drying
Microspheres Are Allowed Drug

6. Drying
Microspheres Are Dried

Figure 2. Stepwise workflow of ionic gelation for floating microsphere preparation, depicting polymer—drug dispersion, droplet formation, ionic crosslinking, curing, washing, and drying, with critical process parameters highlighted at each stage.

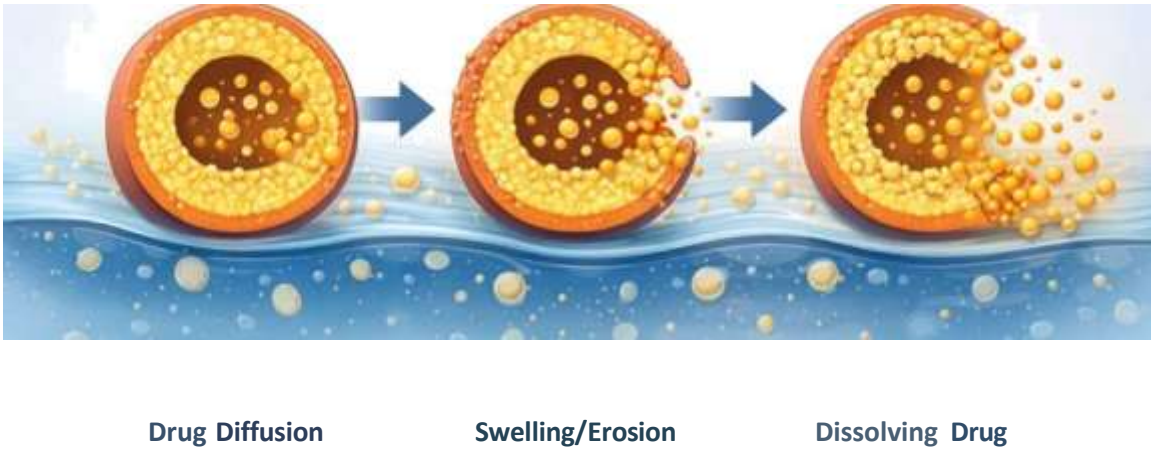


Figure 3. Mcchanistic rcprcscntation of drug rclcasc from floating microsphcrcs, intcgrating polymer swelling, diffusion pathways, matrix relaxatiomerosion, and the corresponding kinetic model interpretations (zero-order, first-order, Higuchi, and Korsmeyer—Peppas).

2. Gastroretentive Drug Delivery Systems: An Overview

Gastroretentive drug delivery systems were developed to prolong the residence of dosage forms within the stomach, thereby enhancing drug absorption, improving bioavailability, and enabling sustained or localized therapeutic action. The stomach represents a highly dynamic environment, and the gastric residence time of conventional oral dosage forms is largely unpredictable. In the fasted state, gastric emptying is governed by the migrating myoelectric complex, which periodically clears gastric contents into the small intestine. In the fed state, gastric emptying is delayed, but it remains dependent on meal composition, caloric density, viscosity, and volume. As a result, drugs administered as immediate-release formulations may be rapidly emptied, leading to incomplete absorption or suboptimal therapeutic profiles.

Several physiological and formulation-related factors influence gastric retention. Physiological factors include gastric motility patterns, pyloric sphincter function, posture, age, gender, and pathological conditions such as diabetes or gastroparesis. Formulation-related factors include dosage form density, size, shape, and swelling behaviour. Drugs that exhibit a narrow absorption window in the upper gastrointestinal tract, reduced solubility at higher intestinal pH, instability in alkaline environments, or a requirement for local gastric action are particularly suitable candidates for gastroretentive delivery approaches.

Multiple gastroretentive strategies have been investigated to overcome the limitations of rapid gastric emptying. Floating systems are designed to remain buoyant on gastric fluid due to their lower density, allowing prolonged gastric residence without interfering with normal gastric emptying of food. Bioadhesive systems rely on polymers that can adhere to the gastric mucosa, thereby resisting gastric clearance. Swelling or expandable systems increase in size upon contact with gastric fluid, preventing passage through the pylorus until sufficient erosion or disintegration occurs. High-density systems, in contrast, are intended to sink and remain in the

lower part of the stomach, although their practical applicability is limited by variability in gastric motility. Among these approaches, floating systems have attracted considerable attention because they are non-invasive, relatively simple to design, and compatible with a wide range of drugs and polymers. Floating drug delivery systems do not require intimate contact with the gastric mucosa, reducing the risk of irritation or localized damage. Their effectiveness depends primarily on maintaining a density lower than that of gastric fluid and ensuring adequate mechanical integrity during the residence period. However, single-unit floating dosage forms such as tablets or capsules may still exhibit variability due to positional effects or sudden gastric emptying events.

Multiparticulate gastroretentive systems, particularly floating microspheres, were introduced to address these limitations. By dispersing multiple low-density units throughout the stomach, microspheres reduce the

likelihood of total dose loss due to premature emptying. This distribution also supports more uniform drug release and minimizes local concentration spikes. From a formulation perspective, multiparticulate systems offer flexibility in controlling particle size, surface characteristics, buoyancy, and release kinetics, making them highly adaptable to different therapeutic requirements.

Overall, gastroretentive drug delivery systems represent a rational strategy for optimizing oral therapy when conventional formulations fail to provide adequate performance. Within this framework, floating microspheres prepared by ionic gelation emerged as a particularly promising platform, combining prolonged gastric retention with controlled release under relatively mild and scalable processing conditions.

3. Floating Drug Delivery Systems

Floating drug delivery systems are designed to remain buoyant in the gastric environment by maintaining a density lower than that of gastric fluid, thereby prolonging gastric residence time and enhancing the effectiveness of oral therapy. The fundamental principle underlying these systems is buoyancy, which allows the dosage form to float on the surface of gastric contents without impeding normal gastric emptying of ingested food. By retaining the formulation in the stomach for extended periods, floating systems can support sustained drug release, improve absorption of drugs with an upper gastrointestinal absorption window, and enhance local therapeutic action in the gastric region.

Floating systems are commonly classified into effervescent and non-effervescent types based on their mechanism of floatation. Effervescent floating systems generate carbon dioxide upon contact with gastric fluid through reactions between acids and bicarbonates. The generated gas becomes entrapped within the polymer matrix, decreasing density and enabling buoyancy. While effective, effervescent systems may exhibit an initial floating lag time and can be sensitive to formulation variables such as gas-generating agent concentration and tablet integrity. Non-effervescent floating systems, in contrast, rely on swelling polymers or low-density materials to achieve buoyancy without gas generation. These systems typically employ hydrophilic polymers that hydrate upon contact with gastric fluid, forming a gel barrier that entraps air and reduces overall density.

The performance of floating drug delivery systems is influenced by several formulation and physiological factors. Formulation parameters include polymer type and concentration, matrix porosity, mechanical strength, and drug loading, all of which affect buoyancy, floating duration, and release behaviour. Physiological factors such as gastric pH, motility, and the presence or absence of food can also modulate system performance. An ideal floating system should exhibit minimal floating lag time, remain buoyant for the intended duration, and maintain structural integrity while releasing drug in a controlled manner.

Although floating tablets and capsules have been widely investigated, they present certain limitations. As single-unit systems, they are more susceptible to unpredictable gastric emptying, positional effects, and mechanical stress caused by gastric contractions. Premature emptying of a single-unit system can result in complete loss of gastroretentive function, potentially compromising therapeutic efficacy. Additionally, single-unit systems may increase the risk of dose dumping if structural failure occurs.

To overcome these limitations, multiparticulate floating systems such as microspheres, beads, and pellets have gained prominence. These systems distribute multiple floating units throughout the stomach, thereby reducing the risk of total dose loss and providing a more consistent release profile. Floating microspheres, in particular, combine the advantages of multiparticulate delivery with controlled-release behaviour and enhanced formulation flexibility. Their small size and low density enable prolonged buoyancy, while polymeric matrices allow precise modulation of drug release kinetics. In summary, floating drug delivery systems constitute a key component of gastroretentive strategies, and multiparticulate floating microspheres offer a refined approach that addresses many of the limitations associated with single-unit formulations. This rationale has driven extensive research into microsphere-based floating systems, particularly those prepared using ionic gelation techniques.

4. Floating Microspheres: Concept and Advantages

Floating microspheres are multiparticulate gastroretentive drug delivery systems specifically engineered to remain buoyant in the gastric environment while providing sustained and controlled drug release. Structurally, these microspheres are typically spherical polymeric particles with a low bulk density, often achieved through the formation of a hollow or porous internal architecture. When introduced into gastric fluid, their density remains lower than that of the surrounding medium, allowing them to float for prolonged periods

without interfering with normal gastric motility or food passage.

The conceptual basis of floating microspheres lies in the integration of two complementary functions: gastric retention through buoyancy and modulation of drug release through polymeric matrix control. Upon contact with gastric fluid, hydrophilic polymers within the microsphere hydrate and form a gel layer that contributes to both buoyancy and controlled diffusion of the encapsulated drug. In some systems, the hollow core or entrapped air pockets further reduce density, reinforcing floatation and prolonging gastric residence time. This dual functionality distinguishes floating microspheres from conventional sustained-release systems that do not actively address gastric retention.

One of the most significant advantages of floating microspheres is their multiparticulate nature. Unlike single-unit dosage forms, microspheres disperse widely throughout the gastric contents, reducing the probability that the entire dose will be expelled during a single gastric emptying event. This distribution contributes to more predictable gastroretentive behaviour and minimizes inter- and intra-subject variability in drug absorption. Additionally, the risk of dose dumping is substantially reduced, as failure or erosion of individual microspheres does not compromise the integrity of the entire dose.

Floating microspheres also offer enhanced formulation flexibility. Particle size, density, surface characteristics, and internal porosity can be modulated through careful selection of polymers and processing conditions. This flexibility allows tailoring of buoyancy duration and drug release profiles to meet specific therapeutic objectives. Furthermore, microspheres can accommodate a wide range of drugs, including those with poor solubility, short half-life, or narrow absorption windows, making them suitable for diverse clinical applications.

From a therapeutic perspective, floating microspheres can improve patient compliance by reducing dosing frequency and maintaining more consistent plasma drug levels. By sustaining drug release in the stomach or proximal intestine, they may also decrease fluctuations in drug concentration that are associated with side effects or reduced efficacy. For drugs intended for local gastric action, floating microspheres provide prolonged exposure at the site of action, potentially enhancing therapeutic outcomes while minimizing systemic exposure. Despite these advantages, the design of floating microspheres presents certain challenges. Achieving an optimal balance between buoyancy and sustained release requires careful control of polymer composition, crosslinking density, and microsphere architecture. Excessive crosslinking may improve mechanical strength but hinder drug release, whereas insufficient crosslinking can compromise structural integrity and buoyancy. Additionally, ensuring reproducibility in particle size and performance remains a critical consideration, particularly for scale-up and industrial manufacturing.

Overall, floating microspheres represent a sophisticated and adaptable gastroretentive delivery platform. Their ability to combine prolonged gastric residence with controlled drug release has positioned them as a promising approach for addressing limitations associated with conventional oral dosage forms. These advantages have driven extensive research into polymeric floating microspheres prepared using mild and versatile techniques such as ionic gelation, which are discussed in subsequent sections.

5. Polymers Used in Floating Microspheres

Polymers play a central role in the design and performance of floating microspheres, as they govern microsphere formation, buoyancy, mechanical integrity, and drug release behavior. In ionic gelation—based systems, polymer selection is particularly critical because gel formation occurs through ionic interactions between functional groups on the polymer chains and multivalent counter-ions. The choice of polymer therefore directly influences crosslinking efficiency, matrix porosity, swelling behavior, and ultimately the sustained-release characteristics of the microspheres.

Natural polymers have been most extensively explored for floating microsphere preparation due to their biocompatibility, biodegradability, low toxicity, and regulatory acceptance. Sodium alginate is among the most widely used polymers in ionic gelation systems. It is a linear polysaccharide composed of mannuronic and guluronic acid residues, and it readily

undergoes gelation in the presence of divalent cations such as calcium. Alginate-based microspheres form a three-dimensional “egg-box” structure upon crosslinking, which can effectively entrap drug molecules while maintaining a relatively low density suitable for buoyancy. Alginate concentration, molecular weight, and the ratio of mannuronic to guluronic acid residues have all been shown to influence ge1 strength, particle size, and drug release profiles.

Chitosan is another important polymer used either alone or in combination with alginate. As a cationic

polysaccharide, chitosan can interact ionically with negatively charged polymers or crosslinking agents, forming polyelectrolyte complexes. When used in floating microspheres, chitosan can enhance mechanical strength, modulate swelling behavior, and impart mucoadhesive properties that may further contribute to gastric retention. Blending chitosan with alginate has been reported to improve microsphere stability and allow finer control over drug release by adjusting the balance between ionic crosslinking and polymer—polymer interactions.

Other natural polymers such as pectin, guar gum, xanthan gum, and gellan gum have also been investigated in ionic gelation—based floating microspheres. Pectin, like alginate, contains carboxyl groups capable of ionic crosslinking with divalent ions, while guar gum and xanthan gum primarily contribute viscosity and swelling properties that influence buoyancy and release kinetics. These polymers are often employed as secondary matrix components or release modifiers rather than primary gelling agents. Their inclusion can reduce microsphere density, enhance floating duration, and slow drug diffusion through increased matrix tortuosity.

Semi-synthetic polymers may also be incorporated to fine-tune microsphere performance. Cellulose derivatives, such as hydroxypropyl methylcellulose, are sometimes added to improve gel stability, control hydration rate, and reduce burst release. Although these polymers do not typically participate directly in ionic crosslinking, they can significantly influence microsphere structure and drug release behavior when used in combination with ionically gelling polymers. The selection of polymers for floating microspheres is guided by several formulation considerations. These include the polymer's ability to form a stable gel under gastric conditions, compatibility with the drug, influence on microsphere density, and responsiveness to ionic crosslinking. The viscosity of the polymer solution affects droplet formation during microsphere preparation, thereby influencing particle size distribution. Additionally, polymer hydration and erosion characteristics determine the dominant drug release mechanism, whether diffusion-controlled, erosion-controlled, or a combination of both.

In summary, polymers are not merely structural components in floating microspheres but active determinants of system performance. Rational selection and combination of polymers enable precise control over buoyancy, mechanical integrity, and sustained-release behaviour. Understanding polymer properties and their interactions within ionic gelation systems is therefore essential for the successful design of floating microspheres for sustained oral drug delivery.

6. Ionic Gelation Technique for Floating Microsphere Preparation

The ionic gelation technique is one of the most widely employed methods for preparing polymeric floating microspheres because it relies on mild processing conditions, avoids harsh organic solvents, and allows precise modulation of microsphere properties through controllable formulation and process variables. The fundamental principle of ionic gelation is based on the formation of a three-dimensional polymeric network via ionic crosslinking between oppositely charged species. Typically, polymers bearing ionizable functional groups undergo rapid gelation upon exposure to multivalent counter-ions, resulting in discrete, gelled microspheres capable of entrapping drug molecules within their matrix.

In a conventional ionic gelation process, the drug is first dispersed or dissolved in an aqueous polymer solution. This solution is then introduced, usually dropwise, into a crosslinking medium containing multivalent ions under continuous stirring. Upon contact with the crosslinking solution, ionic interactions occur instantaneously, leading to the formation of microspheres. The crosslinked particles are allowed to cure for a defined period to strengthen the gel network, followed by washing to remove excess ions and unentrapped drug, and finally drying to obtain free-flowing microspheres. The simplicity of this sequence, combined with its adaptability to various polymers and drugs, has made ionic gelation particularly attractive for floating microsphere fabrication.

The choice of polymer—ion pair is central to successful ionic gelation. Anionic polymers such as alginate or pectin are commonly crosslinked using divalent cations like calcium, zinc, or barium, whereas cationic polymers such as chitosan may undergo gelation through interaction with multivalent anions or polyanionic counter-polymers. The strength and density of crosslinking depend on the valency and concentration of the crosslinking ion, which in turn influence microsphere rigidity, porosity, and drug release characteristics. Higher crosslinker concentrations generally produce denser matrices with reduced swelling and slower drug diffusion, whereas lower concentrations may yield weaker structures with faster release and reduced mechanical stability.

Several process parameters critically affect microsphere formation and performance. Polymer concentration plays a decisive role in determining solution viscosity, droplet formation, and particle size. Low polymer concentrations may result in poorly formed microspheres with low entrapment efficiency, whereas excessively viscous solutions can hinder droplet breakup and produce irregular particles. Stirring speed during gelation influences shear forces acting on forming droplets; higher speeds typically reduce particle size but may also increase the risk of shape deformation or surface erosion. Curing time controls the extent of crosslinking, with longer curing generally enhancing mechanical strength but potentially restricting drug release. Drying method is another important consideration in ionic gelation—based floating microsphere preparation. Air drying, oven drying, and lyophilization have all been reported in the literature. Drying conditions influence microsphere density, internal porosity, and buoyancy. For floating microspheres, controlled drying that preserves internal voids or porosity is desirable, as these features contribute to reduced density and prolonged floatation. Excessive drying or collapse of the gel structure may increase density and compromise buoyancy.

One of the notable advantages of ionic gelation is its compatibility with thermolabile and moisture-sensitive drugs, as the process typically occurs at ambient temperature and physiological pH ranges. Additionally, the aqueous nature of the process minimizes residual solvent concerns and supports regulatory acceptance. The technique also allows straightforward incorporation of polymer blends, enabling fine-tuning of microsphere properties through synergistic interactions between polymers.

Despite these advantages, ionic gelation presents certain challenges. The method can be sensitive to variations in ionic strength and pH of the crosslinking medium, leading to batch-to-batch variability if process conditions are not tightly controlled. Scale-up may be complicated by difficulties in maintaining uniform droplet formation and consistent crosslinking in larger volumes. Furthermore, rapid surface gelation can sometimes trap drug near the microsphere surface, contributing to an initial burst release if formulation parameters are not optimized.

Overall, ionic gelation represents a robust and versatile technique for the preparation of floating microspheres. Its ability to produce low-density, polymeric particles with controllable release characteristics under mild conditions underpins its widespread application in gastroretentive drug delivery research. Careful optimization of formulation and process variables is essential to fully exploit the advantages of this technique while minimizing its limitations.

7. Factors Affecting Formulation and Performance of Floating Microspheres

The performance of floating microspheres prepared by ionic gelation is determined by a complex interplay of formulation variables and process parameters. These factors collectively influence critical quality attributes such as particle size, density, buoyancy, drug loading, entrapment efficiency, and in vitro release behaviour. Understanding and controlling these variables is essential for designing a reproducible and effective gastroretentive microsphere system.

Polymer concentration is one of the most influential formulation parameters. Increasing polymer concentration generally raises solution viscosity, which can lead to the formation of larger microspheres during droplet generation. Higher polymer content typically enhances entrapment efficiency and mechanical strength by creating a denser polymeric network. However, excessively high polymer concentrations may reduce drug diffusion, prolong release beyond the desired duration, and compromise buoyancy by increasing microsphere density. Conversely, low polymer concentrations can result in fragile microspheres with poor structural integrity and rapid drug release.

The type and concentration of crosslinking agent also play a critical role. Higher concentrations of multivalent ions increase crosslinking density, producing rigid microspheres with reduced swelling and slower drug release. While this may be advantageous for sustained delivery, excessive crosslinking can decrease drug entrapment and reduce buoyancy due to increased density. Selection of the crosslinking ion, based on its valency and binding affinity, further influences microsphere properties and release kinetics.

Process-related factors such as stirring speed and curing time significantly affect microsphere formation. Increased stirring speed enhances shear forces, resulting in smaller particle sizes and narrower size distributions. However, overly high speeds may cause irregular shapes or surface erosion. Curing time determines the extent of ionic crosslinking; insufficient curing can yield weak microspheres prone to disintegration, whereas prolonged curing may restrict polymer relaxation and hinder drug release.

Drug-related factors, including solubility and drug—polymer interactions, also influence microsphere

performance. Drugs with high aqueous solubility may diffuse out of the polymer matrix during gelation, reducing entrapment efficiency and increasing initial burst release. In contrast, poorly soluble drugs may be retained more effectively within the matrix but could exhibit slower and incomplete release. Compatibility between drug and polymer is therefore crucial to achieving balanced encapsulation and release behaviour.

Drying conditions affect microsphere density, porosity, and buoyancy. Rapid or harsh drying may collapse internal pores, increasing density and reducing floating duration. Controlled drying methods that preserve internal voids are preferred for floating systems. Additionally, the incorporation of secondary polymers or release modifiers can influence swelling behaviour, matrix integrity, and release kinetics, allowing further optimization of microsphere performance.

In summary, the formulation and performance of floating microspheres are highly sensitive to both material selection and processing conditions. Systematic optimization, often supported by statistical or quality-by-design approaches, is essential to identify robust formulation windows that deliver consistent buoyancy and sustained release. Careful control of these factors underpins the successful development of ionic gelation—based floating microsphere systems for oral drug delivery.

8. *in Vitro* Evaluation of Floating Microspheres

In vitro evaluation forms the foundation for assessing the quality, performance, and reproducibility of floating microspheres prepared by ionic gelation. These studies are essential to establish whether the microspheres possess the intended physicochemical characteristics, buoyancy behaviour, and sustained drug release profile before advancing toward in vivo investigation. Standardized in vitro tests also enable meaningful comparison between formulations reported across the literature.

Micromeritic properties are typically evaluated as an initial step to understand powder handling and flow behaviour. Parameters such as particle size distribution, bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose provide insight into flowability and packing characteristics. Particle size is a particularly critical attribute, as it influences buoyancy, drug release kinetics, and gastric distribution. Microspheres intended for gastroretentive delivery generally fall within a size range that balances prolonged floatation with uniform dispersion in gastric contents.

Percentage yield, drug loading, and entrapment efficiency are routinely determined to evaluate formulation efficiency. Drug loading reflects the amount of drug incorporated relative to total microsphere mass, whereas entrapment efficiency indicates the fraction of the initial drug successfully encapsulated within the polymeric matrix. These parameters are influenced by polymer concentration, crosslinking density, drug solubility, and curing conditions. High entrapment efficiency is desirable for dose uniformity and to minimize drug loss during processing.

Buoyancy-related studies are central to the evaluation of floating microspheres. Floating lag time and total floating duration are typically measured by dispersing microspheres in simulated gastric fluid and observing their behaviour under mild agitation. An ideal floating microsphere system should exhibit negligible or no floating lag time and remain buoyant for several hours. Quantitative buoyancy assessment is often performed by calculating the percentage of microspheres remaining afloat over time, which provides a more objective measure of floating performance. Swelling studies offer insight into polymer hydration and matrix expansion, which directly affect buoyancy and drug release. Swelling index is determined by measuring the weight gain of microspheres upon immersion in simulated gastric fluid over time. Controlled and moderate swelling is generally preferred, as excessive swelling may lead to rapid erosion or loss of mechanical integrity, while insufficient swelling can restrict drug diffusion and reduce release rates.

Surface morphology and internal structure are commonly examined using microscopic techniques. Scanning electron microscopy is widely employed to assess particle shape, surface texture, and porosity. Floating microspheres often exhibit spherical morphology with surface roughness or pores that contribute to buoyancy and drug release. Internal porosity, when preserved during drying, plays a key role in reducing density and maintaining floatation.

In vitro drug release studies are conducted using dissolution apparatus under simulated gastric conditions, typically employing acidic media. Release profiles are analyzed to determine the extent and rate of drug release over time. The data are frequently fitted to kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer—Peppas equations to elucidate the dominant release mechanism. In many ionic gelation—based microsphere systems, drug release is governed by a combination of diffusion through the hydrated polymer matrix and gradual erosion or relaxation of the polymer network.

Collectively, these in vitro evaluation parameters provide a comprehensive understanding of floating microsphere behaviour and performance. They serve as critical decision-making tools for formulation optimization and play a pivotal role in establishing correlations between formulation variables and functional outcomes. Robust in vitro characterization is therefore indispensable for the rational development of floating microspheres intended for sustained oral drug delivery.

9. Advantages and Limitations of Ionic Gelation—Based Floating Microspheres

Ionic gelation—based floating microspheres offer several notable advantages that have contributed to their widespread investigation in gastroretentive drug delivery research. One of the most significant benefits of this technique is the use of mild processing conditions. Because ionic gelation typically occurs in aqueous media at ambient temperatures, it is well suited for thermolabile and chemically sensitive drugs. The avoidance of harsh organic solvents and high-energy input also improves safety, reduces residual solvent concerns, and enhances regulatory acceptability.

Another key advantage is the simplicity and versatility of the method. Ionic gelation does not require complex equipment and can be readily adapted to a wide range of polymers, particularly naturally derived polysaccharides. This flexibility allows formulation scientists to tailor microsphere properties such as particle size, density, and drug release behaviour through rational selection of polymer type, polymer concentration, and crosslinking ion. The technique also facilitates the formation of low-density, porous structures that are essential for prolonged buoyancy in the gastric environment. Additionally, the multiparticulate nature of floating microspheres reduces the risk of dose dumping and contributes to more predictable gastroretentive behaviour compared with single-unit dosage forms.

Despite these advantages, ionic gelation—based floating microspheres also present certain limitations. One of the primary challenges is sensitivity to variations in process conditions, particularly ionic strength, pH, and crosslinker concentration. Minor deviations in these parameters can lead to significant changes in microsphere properties, resulting in batch-to-batch variability if strict control is not maintained. Rapid surface gelation during microsphere formation may also lead to uneven drug distribution, increasing the risk of an initial burst release. Scale-up and industrial translation represent additional challenges. Achieving uniform droplet formation and consistent crosslinking in larger volumes can be difficult, potentially affecting particle size distribution and reproducibility. Furthermore, some ionically crosslinked polymers may exhibit reduced stability in environments with high ionic strength, which can influence long-term performance. In summary, ionic gelation—based floating microspheres combine practical advantages with specific technical challenges. Careful optimization, process control, and formulation design are essential to maximize their benefits while mitigating limitations associated with variability and scalability.

10. Future Perspectives and Research Directions

Future research on ionic gelation—based floating microspheres is expected to focus on enhancing formulation robustness, translational potential, and clinical relevance. One of the most promising directions involves the rational use of polymer blends and multilayered microsphere systems. Combining polymers with complementary properties can improve mechanical strength, buoyancy, and control over drug release while minimizing individual polymer limitations. The strategic use of polyelectrolyte complexes may further refine matrix architecture and enable more predictable release behaviour under gastric conditions.

The adoption of quality-by-design principles is likely to play an increasingly important role in floating microsphere development. Systematic identification of critical material attributes and critical process parameters, supported by statistical design of experiments, can help establish robust design spaces and reduce batch-to-batch variability. Such approaches are particularly valuable for ionic gelation systems, which are inherently sensitive to formulation and processing variables. Enhanced process understanding will also facilitate scale-up and support regulatory acceptance.

Advances in characterization techniques are expected to improve understanding of microsphere structure—function relationships. High-resolution imaging, porosity analysis, and advanced thermal and spectroscopic methods can provide deeper insight into polymer crosslinking, internal architecture, and drug—polymer interactions. These data may help optimize microsphere design to balance buoyancy and sustained release more effectively.

Another critical area for future investigation is the development of stronger in vitro—in vivo correlations. While in vitro evaluation methods are well established, translating buoyancy and release behaviour into

reliable predictions of in vivo gastric residence and pharmacokinetic performance remains challenging. Improved biorelevant dissolution models and dynamic gastric simulation systems may bridge this gap and accelerate clinical translation.

Finally, efforts toward scalable manufacturing and industrial feasibility will be essential for broader adoption. Continuous or semi-continuous production methods, improved droplet-generation technologies, and process analytical tools could support consistent large-scale production of floating microspheres. Collectively, these research directions highlight the potential for ionic gelation—based floating microspheres to evolve from experimental systems into clinically and commercially viable gastroretentive drug delivery platforms.

11. Conclusion

Floating microspheres prepared by ionic gelation represent a well-established and versatile approach for sustained oral drug delivery, particularly for drugs that benefit from prolonged gastric residence and controlled release in the upper gastrointestinal tract. By integrating buoyancy with polymer-mediated release control, these multiparticulate systems effectively address several limitations associated with conventional oral dosage forms, including rapid gastric emptying, fluctuating drug plasma levels, and the risk of dose dumping seen with single-unit formulations. The review highlighted the scientific rationale underlying gastroretentive delivery and emphasized floating microspheres as a refined strategy within this domain. The ionic gelation technique emerged as a key enabling method due to its operational simplicity, mild processing conditions, and compatibility with a broad range of biocompatible polymers.

Careful selection of polymers, crosslinking ions, and processing parameters was shown to be critical for achieving the desired balance between buoyancy, mechanical stability, and sustained drug release. In vitro evaluation studies remain indispensable for assessing microsphere quality, providing insights into micromeritic properties, buoyancy behavior, swelling dynamics, surface morphology, and release kinetics. Despite their advantages, ionic gelation—based floating microspheres are not without limitations. Sensitivity to formulation and process variations, challenges in large-scale production, and the need for stronger in vitro—in vivo correlations continue to restrict seamless translation to clinical and commercial settings. Addressing these challenges through systematic optimization, quality-by-design frameworks, and advanced characterization techniques will be essential for future progress. Overall, floating microspheres prepared by ionic gelation continue to offer significant promise as gastroretentive drug delivery systems. With ongoing refinement in formulation design, process control, and translational research, these systems have the potential to contribute meaningfully to the development of more effective and patient-friendly oral therapies.

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