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Oral Gastroretentive Mucoadhesive Drug Delivery Systems: Role Of Polymeric Carriers, Bioadhesion Mechanisms, And Release Modulation

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Abstract

Oral gastroretentive mucoadhesive drug delivery systems have emerged as a promising strategy to overcome the limitations associated with conventional oral dosage forms, particularly for drugs exhibiting narrow absorption windows, short biological half-lives, or pH-dependent solubility. By prolonging gastric residence time and maintaining intimate contact with the gastric mucosa, these systems enhance drug bioavailability, reduce dosing frequency, and improve therapeutic efficacy. Among various gastroretentive approaches, mucoadhesive microspheres have gained significant attention due to their multiparticulate nature, reduced risk of dose dumping, and ability to provide controlled and predictable drug release. This review comprehensively discusses the role of polymeric carriers—both natural and synthetic—in the design of oral gastroretentive mucoadhesive drug delivery systems, with emphasis on their physicochemical properties, mucoadhesive potential, and release-modulating capabilities. The fundamental mechanisms of bioadhesion, including polymer–mucus interactions and contributing theoretical models, are critically examined. Additionally, formulation strategies, multifactorial optimization approaches, and key evaluation parameters such as micromeritic properties, bioadhesive strength, swelling behaviour, and in vitro drug release kinetics are systematically reviewed. Finally, current challenges and future perspectives in the development of gastroretentive mucoadhesive microspheres are highlighted, underscoring their potential for improving oral drug delivery and expanding clinical applicability.

Keywords

Gastroretentive drug delivery**,** Mucoadhesive microspheres**,** Polymeric carriers**,** Bioadhesion mechanisms**,** Controlled drug release

Introduction and Background

Oral drug delivery remains the most widely preferred route for therapeutic administration due to its convenience, patient compliance, cost-effectiveness, and ease of large-scale manufacturing. Despite these advantages, conventional oral dosage forms often face significant physiological and biopharmaceutical challenges that limit their therapeutic efficiency. One of the most critical limitations is the unpredictable gastric residence time of dosage forms, which directly affects drug absorption, particularly for drugs that exhibit a narrow absorption window in the upper gastrointestinal tract, instability at intestinal pH, or reduced solubility at higher pH values. Rapid gastric emptying can lead to subtherapeutic drug levels, frequent dosing, and poor bioavailability, ultimately compromising treatment outcomes. These challenges have driven extensive research into advanced oral drug delivery systems capable of prolonging gastric retention and providing controlled and predictable drug release [1-4].

Gastroretentive drug delivery systems (GRDDS) were developed as a strategic approach to overcome the limitations associated with conventional oral formulations. These systems are specifically designed to remain in the stomach for an extended period, thereby enhancing drug absorption, improving bioavailability, and maintaining sustained plasma drug concentrations. Several gastroretentive approaches have been explored, including floating systems, high-density systems, expandable systems, raft-forming systems, superporous hydrogels, and mucoadhesive systems. Among these, mucoadhesive drug delivery systems have gained considerable attention due to their ability to adhere to the gastric mucosa, resist gastric emptying forces, and localize the drug at the site of absorption. By forming intimate contact with the mucosal surface, mucoadhesive systems enhance drug residence time and facilitate improved drug permeation across the gastric epithelium [5-8].

Mucoadhesive microspheres represent a particularly promising class of gastroretentive systems, combining the advantages of multiparticulate delivery with strong bioadhesive properties. Multiparticulate systems offer several benefits over single-unit dosage forms, including reduced risk of dose dumping, uniform distribution within the stomach, improved safety profile, and reproducible drug release kinetics. When engineered as mucoadhesive microspheres, these systems can effectively interact with the mucus layer lining the gastric epithelium, enabling prolonged retention and sustained drug release. This makes them especially suitable for drugs requiring extended gastric exposure, drugs with short biological half-lives, and drugs intended for local or systemic effects following gastric absorption [6, 9-14].

The success of gastroretentive mucoadhesive microspheres largely depends on the selection and optimization of polymeric carriers. Polymers play a central role in determining the physicochemical properties, mucoadhesive strength, swelling behavior, drug encapsulation efficiency, and release characteristics of microsphere-based delivery systems. Both natural and synthetic polymers have been extensively investigated for this purpose. Natural polymers such as chitosan, sodium alginate, pectin, guar gum, xanthan gum, and gelatin are valued for their biocompatibility, biodegradability, low toxicity, and inherent mucoadhesive properties. These polymers often contain functional groups capable of forming hydrogen bonds or electrostatic interactions with mucin glycoproteins, thereby enhancing bioadhesion. However, natural polymers may suffer from batch-to-batch variability and limited mechanical strength, which can affect formulation reproducibility [15-19].

Synthetic polymers, including hydroxypropyl methylcellulose (HPMC), carbopol, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), and Eudragit grades, offer greater structural consistency, tunable physicochemical properties, and improved mechanical stability. These polymers allow precise modulation of swelling behaviour, viscosity, and drug release profiles. In many formulations, a combination of natural and synthetic polymers is employed to achieve synergistic effects, balancing strong mucoadhesion with optimal mechanical strength and controlled release performance. The rational selection and proportioning of these polymers form the foundation of successful gastroretentive mucoadhesive microsphere design [15-19]. Bioadhesion, which underpins the gastroretentive capability of mucoadhesive systems, is a complex and multifactorial phenomenon. Several theories have been proposed to explain the mechanisms of mucoadhesion, including the wetting theory, diffusion theory, adsorption theory, electronic theory, and fracture theory. In the gastric environment, mucoadhesion typically involves an initial wetting and swelling

phase, followed by polymer chain interpenetration with the mucus layer and the formation of secondary chemical bonds such as hydrogen bonding, van der Waals forces, and electrostatic interactions. The extent and durability of mucoadhesion are influenced by polymer molecular weight, degree of crosslinking, chain flexibility, surface charge, hydration rate, and environmental factors such as pH and ionic strength. A thorough understanding of these mechanisms is essential for designing microspheres with reliable and sustained gastric adhesion [20-27].

In addition to gastric retention, controlled and predictable drug release is a critical requirement for gastroretentive mucoadhesive systems. Release modulation from microspheres is governed by multiple factors, including polymer swelling, matrix erosion, diffusion of drug molecules through the polymer network, and, in some cases, polymer relaxation or degradation. By carefully manipulating formulation variables such as polymer type, polymer concentration, crosslinking density, and microsphere size, it is possible to tailor drug release kinetics to achieve sustained or controlled release over extended periods. In vitro drug release studies, coupled with kinetic modeling using mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations, provide valuable insights into the underlying release mechanisms and formulation performance [20-32].

Comprehensive evaluation of gastroretentive mucoadhesive microspheres also requires detailed assessment of micromeritic properties, including particle size, size distribution, bulk and tapped density, Carr's index, Hausner ratio, and angle of repose. These parameters are crucial for predicting flow behavior, packing properties, and uniformity during capsule filling or tableting. Additionally, in vitro bioadhesion studies, swelling index determination, and ex vivo mucoadhesion testing using gastric mucosa models are commonly employed to assess the adhesive potential and gastric retention capability of microspheres. Such multifaceted characterization ensures that the developed systems meet both pharmaceutical quality standards and therapeutic performance expectations [28-32].

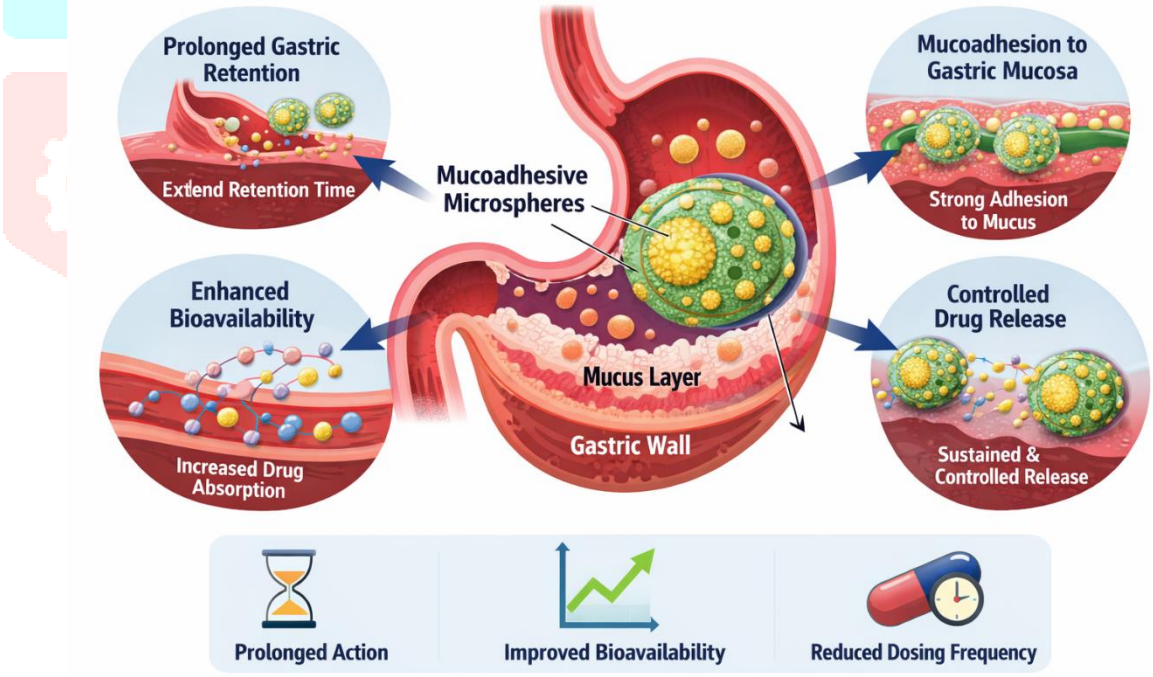

Figure 1. Schematic representation of gastroretentive mucoadhesive microspheres adhering to the gastric mucosa and providing sustained drug release.

In this context, the present review aims to provide a comprehensive and critical overview of oral gastroretentive mucoadhesive drug delivery systems, with particular emphasis on the role of polymeric carriers, mechanisms of bioadhesion, and strategies for release modulation. By integrating insights from formulation science, polymer chemistry, and drug release kinetics, this review highlights current advances, formulation challenges, and future opportunities in the design of mucoadhesive microsphere-based gastroretentive systems. The subsequent sections will systematically discuss polymeric materials used in

these systems, mechanistic aspects of mucoadhesion, formulation and optimization strategies, evaluation parameters, and emerging trends shaping the future of gastroretentive drug delivery research.

Polymeric Carriers Used in Gastroretentive Mucoadhesive Drug Delivery Systems

Polymeric carriers form the structural and functional backbone of gastroretentive mucoadhesive drug delivery systems, as they directly govern gastric residence time, mucoadhesive strength, drug encapsulation efficiency, and release modulation. The choice of polymer is therefore a critical determinant of formulation success. An ideal polymeric carrier for gastroretentive mucoadhesive microspheres should be biocompatible, non-toxic, chemically stable in the acidic gastric environment, capable of forming strong interactions with gastric mucus, and able to provide predictable and reproducible drug release profiles. Both natural and synthetic polymers, as well as their combinations, have been extensively explored to fulfil these requirements [8, 33-37].

Natural polymers have gained considerable attention due to their inherent biodegradability, biocompatibility, and favourable safety profiles. Chitosan is one of the most extensively studied natural polymers for gastroretentive mucoadhesive systems. Its cationic nature enables strong electrostatic interactions with the negatively charged sialic acid residues of mucin, resulting in enhanced mucoadhesion. In acidic gastric conditions, chitosan undergoes protonation, which further improves its solubility and adhesive behaviour. Chitosan-based microspheres have demonstrated prolonged gastric retention and sustained drug release, making them suitable for drugs requiring extended gastric exposure. However, chitosan's solubility is pH-dependent, and its mechanical strength may be insufficient when used alone, necessitating blending with other polymers [38-42].

Sodium alginate is another widely employed natural polymer, particularly valued for its gel-forming ability in the presence of divalent cations such as calcium ions. Alginate-based microspheres are commonly prepared using ionotropic gelation techniques, producing spherical, uniform particles with good encapsulation efficiency. Alginate contributes to gastroretention by swelling in gastric fluid and forming a viscous gel layer that resists gastric emptying. However, alginate alone exhibits relatively weak mucoadhesive properties, and its rapid erosion in acidic environments can limit sustained release performance. To overcome these limitations, alginate is frequently combined with mucoadhesive polymers such as chitosan or Carbopol [40, 43, 44].

Other natural polymers such as pectin, guar gum, xanthan gum, gelatin, and tragacanth have also been explored for gastroretentive applications. Pectin exhibits pH-sensitive gelling behavior and can contribute to controlled drug release, while guar gum and xanthan gum provide high viscosity and swelling capacity, enhancing gastric retention. Gelatin, a protein-based polymer, offers good film-forming properties and biocompatibility, although its thermal sensitivity and potential for microbial growth require careful formulation control. Despite their advantages, natural polymers often suffer from batch-to-batch variability, limited mechanical strength, and susceptibility to enzymatic degradation, which can affect formulation reproducibility and long-term stability [40, 43, 44].

Synthetic polymers provide greater control over physicochemical properties and structural consistency, making them highly suitable for pharmaceutical applications. Hydroxypropyl methylcellulose (HPMC) is one of the most widely used synthetic polymers in gastroretentive systems. Its hydrophilic nature allows rapid hydration and swelling, forming a gel barrier that controls drug diffusion and matrix erosion. Different viscosity grades of HPMC enable fine-tuning of drug release kinetics and swelling behaviour. HPMC also contributes indirectly to mucoadhesion by increasing residence time through swelling and viscosity enhancement. Carbopol, a high molecular weight crosslinked polyacrylic acid polymer, is well known for its exceptional mucoadhesive properties. The presence of numerous carboxyl groups allows extensive hydrogen bonding with mucin, resulting in strong and prolonged adhesion to gastric mucosa. Carbopol-based microspheres exhibit high swelling capacity and controlled drug release; however, excessive swelling may lead to premature matrix erosion or dose dumping if not properly optimized. Therefore, carbopol is often used in low concentrations or in combination with other polymers to balance adhesion and release characteristics [45-49].

Polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) are commonly used as stabilizers and matrix-forming agents in microsphere formulations. PVA provides structural integrity and improves particle sphericity during microsphere preparation, while PVP enhances drug solubility and uniform drug distribution within the polymer matrix. Although these polymers exhibit limited intrinsic mucoadhesion, they play a supportive role in improving formulation stability and release uniformity. Eudragit polymers, particularly cationic grades such as Eudragit RL and RS, have also been investigated for gastroretentive applications due to their pH-independent swelling and permeability-controlling properties [50-52].

In recent years, polymer blending and composite systems have emerged as an effective strategy to overcome the limitations associated with single-polymer systems. By combining natural and synthetic polymers, it is possible to achieve synergistic effects that enhance mucoadhesion, mechanical strength, and controlled release simultaneously. For example, chitosan–alginate microspheres benefit from electrostatic interactions between oppositely charged polymers, resulting in improved structural integrity and sustained drug release. Similarly, carbopol–HPMC blends offer a balance between strong mucoadhesion and controlled swelling, leading to optimized gastroretentive performance. Such multifactorial polymeric systems enable precise modulation of formulation characteristics through rational design and optimization [53-56].

Table 1. Common natural and synthetic polymers used in gastroretentive mucoadhesive drug delivery systems and their functional roles.

Polymer Type	**Polymer Name**	**Key Properties**	**Role in Gastroretentive Mucoadhesive Systems**
Natural polymer	Chitosan	Cationic, biodegradable, pH-sensitive, high mucoadhesion	Strong electrostatic interaction with gastric mucin; enhances bioadhesion and gastric retention
Natural polymer	Sodium alginate	Anionic, gel-forming, biocompatible	Swelling and gel formation in gastric fluid; contributes to controlled release
Natural polymer	Pectin	Hydrophilic, pH-responsive, biodegradable	Matrix formation and modulation of drug release
Natural polymer	Guar gum	High viscosity, swelling polymer	Prolongs gastric residence by viscosity enhancement
Natural polymer	Xanthan gum	Hydrophilic, stable over wide pH range	Sustained release and improved matrix integrity
Natural polymer	Gelatin	Biocompatible, film-forming	Structural support and controlled drug encapsulation
Synthetic polymer	Hydroxypropyl methylcellulose (HPMC)	Hydrophilic, swellable, viscosity-controlled	Release retardation and matrix stability
Synthetic polymer	Carbopol	High molecular weight, cross-linked polyacrylic acid	Strong mucoadhesion through hydrogen bonding
Synthetic polymer	Polyvinyl alcohol (PVA)	Water-soluble, stabilizing agent	Improves microsphere formation and surface smoothness
Synthetic polymer	Polyvinylpyrrolidone (PVP)	Hydrophilic, solubilizing agent	Enhances drug dispersion and release uniformity

Synthetic polymer	Eudragit (RL/RS)	pH-independent, permeable	Controlled release and mechanical strength
Polymer blend	Chitosan + Alginate	Polyelectrolyte complex	Enhanced adhesion and sustained release
Polymer blend	Carbopol + HPMC	Synergistic swelling and adhesion	Balanced mucoadhesion and release control

Beyond polymer selection, the physicochemical properties of polymers, including molecular weight, degree of substitution, crosslinking density, and surface charge, significantly influence formulation performance. High molecular weight polymers generally exhibit stronger mucoadhesion due to increased chain entanglement with mucus, while excessive crosslinking may reduce polymer flexibility and limit adhesive interactions. Similarly, polymer hydration rate affects initial adhesion and swelling behaviour, which in turn influences gastric retention and drug release. These parameters must be carefully optimized to ensure consistent and reproducible performance of gastroretentive microspheres [14, 57-59].

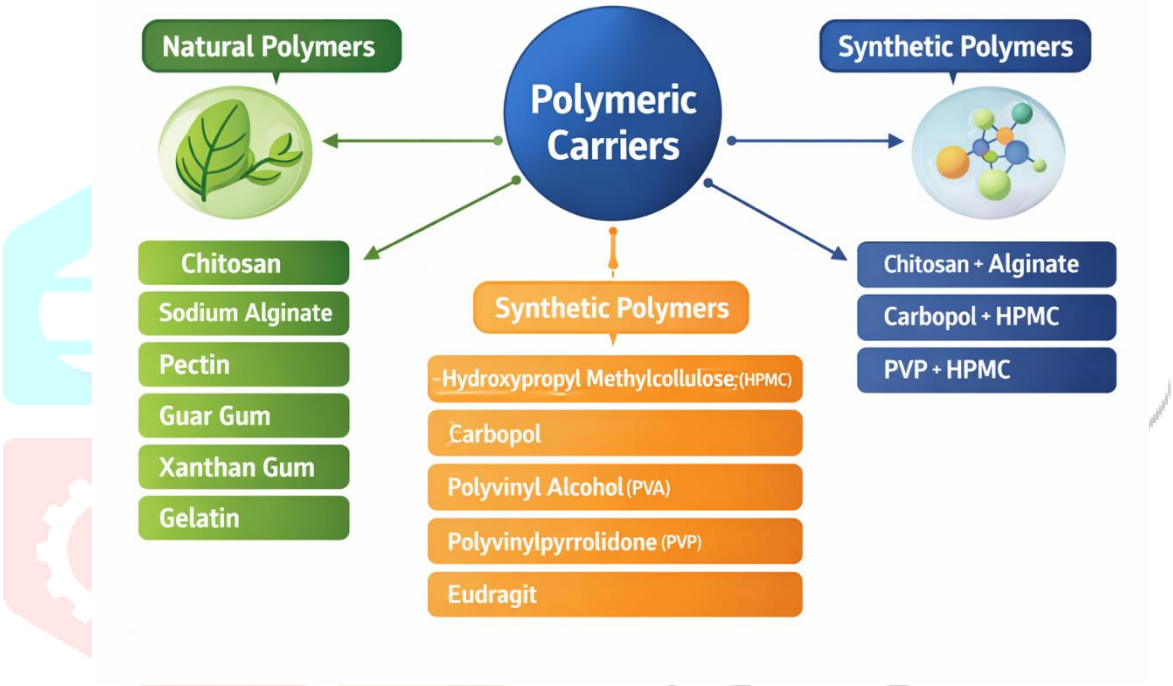

Figure 2. Classification of polymeric carriers used in gastroretentive mucoadhesive microspheres based on origin and functional properties.

In summary, polymeric carriers play a pivotal role in the design and performance of oral gastroretentive mucoadhesive drug delivery systems. Natural polymers offer biocompatibility and inherent adhesion, while synthetic polymers provide structural reliability and controlled release capabilities. The strategic combination of these polymers enables the development of robust, efficient, and patient-friendly gastroretentive microsphere formulations. The next section will focus on the fundamental mechanisms of mucoadhesion and their relevance to gastric retention and drug delivery performance [14, 57-59].

Mechanisms of Bioadhesion in Gastroretentive Mucoadhesive Systems

Bioadhesion is the defining characteristic that enables mucoadhesive drug delivery systems to achieve prolonged gastric residence and enhanced therapeutic performance. In the context of oral gastroretentive systems, bioadhesion refers to the ability of a dosage form or polymeric carrier to adhere to the mucus layer covering the gastric epithelium. This interaction allows the formulation to resist gastric motility and emptying, thereby maintaining close contact with the site of drug absorption for extended periods. Understanding the mechanisms governing bioadhesion is therefore essential for the rational design and optimization of mucoadhesive microspheres [60-62].

The gastric mucus layer is a viscoelastic, hydrated gel composed primarily of mucin glycoproteins, water, electrolytes, enzymes, and lipids. Mucin molecules possess a high density of hydroxyl, carboxyl, and sialic

acid groups, imparting an overall negative charge to the mucus layer under physiological conditions. This biochemical composition creates multiple opportunities for interaction with polymeric carriers, particularly those containing complementary functional groups or charge characteristics. The thickness, turnover rate, and rheological properties of gastric mucus vary depending on physiological conditions, disease state, and feeding patterns, all of which can influence the extent and duration of mucoadhesion.

Several classical theories have been proposed to explain the phenomenon of bioadhesion, each describing different aspects of the adhesion process. In practice, mucoadhesion is considered a multifactorial event involving the simultaneous contribution of multiple mechanisms rather than a single dominant theory. The wetting theory is one of the earliest concepts and is particularly relevant for liquid or semi-solid mucoadhesive systems. According to this theory, effective adhesion requires the formulation to spread easily over the mucosal surface, thereby maximizing the area of contact. The degree of wetting is influenced by surface tension, contact angle, and polymer hydrophilicity. In microsphere-based systems, rapid hydration and surface wetting facilitate initial contact with the mucus layer, creating favourable conditions for subsequent adhesive interactions [60, 62-66].

The diffusion theory emphasizes the interpenetration of polymer chains with mucin chains at the molecular level. Once the polymer comes into contact with the hydrated mucus layer, polymer chains begin to diffuse into the mucin network, forming an entangled interfacial region. The depth of interpenetration depends on factors such as polymer molecular weight, chain flexibility, crosslinking density, and contact time. Flexible, linear polymer chains with high molecular weight tend to exhibit stronger mucoadhesion due to enhanced chain entanglement. This theory is particularly relevant for hydrophilic polymers such as chitosan, carbopol, and cellulose derivatives, which readily swell and interact with mucus [62-66].

The adsorption theory describes mucoadhesion as the result of secondary chemical interactions formed at the polymer–mucus interface. These interactions include hydrogen bonding, van der Waals forces, hydrophobic interactions, and electrostatic attractions. Hydrogen bonding plays a dominant role in many mucoadhesive systems, especially those containing hydroxyl, carboxyl, or amine functional groups. Electrostatic interactions are especially significant for charged polymers; for example, cationic polymers such as chitosan exhibit strong attraction to negatively charged mucin, resulting in enhanced adhesive strength. Although these interactions are individually weak, their cumulative effect can produce substantial and durable adhesion [65, 67-69].

The electronic theory proposes that bioadhesion occurs due to electron transfer between the polymer and mucus, leading to the formation of an electrical double layer at the interface. This results in attractive electrostatic forces that contribute to adhesion. While this theory is less commonly emphasized in pharmaceutical applications, it may partially explain the strong adhesion observed with oppositely charged polymer–mucus systems. The fracture theory, on the other hand, focuses on the mechanical aspects of adhesion and describes bioadhesion in terms of the force required to separate the polymer from the mucosal surface. This theory is particularly useful for quantifying mucoadhesive strength during experimental evaluation and comparing the adhesive performance of different formulations [62-66].

In gastroretentive mucoadhesive microspheres, the bioadhesion process typically occurs in two stages. The first stage involves initial contact and wetting, during which the microspheres hydrate and adhere loosely to the mucus layer. The second stage involves consolidation of adhesion, characterized by polymer swelling, chain interpenetration, and the formation of chemical bonds. The balance between hydration and adhesion is critical; excessive hydration may lead to over-swelling and reduced adhesive strength, whereas insufficient hydration can limit polymer chain mobility and interaction with mucin [8, 33, 37, 70, 71].

Several formulation-related and physiological factors influence the effectiveness of bioadhesion. Polymer-related factors include molecular weight, concentration, degree of crosslinking, surface charge, and functional group availability. Higher polymer concentrations generally enhance mucoadhesion by increasing the number of available interaction sites; however, excessively high concentrations may result in rigid matrices with limited chain mobility. Similarly, moderate crosslinking can improve mechanical stability, whereas excessive crosslinking may hinder polymer swelling and interpenetration. Physiological

factors such as gastric pH, mucus turnover rate, presence of food, and enzymatic activity also play a significant role in determining the duration and strength of mucoadhesion [1, 35, 36, 72].

Table 2. Theories of bioadhesion and their relevance to gastroretentive mucoadhesive drug delivery systems.

Theory of Bioadhesion	Basic Principle	Relevance to Gastroretentive Systems
Wetting theory	Adhesion depends on spreading of formulation over mucosa	Important for initial contact and hydration of microspheres
Diffusion theory	Interpenetration of polymer chains with mucin	Major contributor to long-term mucoadhesion
Adsorption theory	Formation of secondary chemical bonds	Hydrogen bonding and van der Waals forces stabilize adhesion
Electronic theory	Electron transfer between polymer and mucus	Explains electrostatic attraction in charged polymers
Fracture theory	Force required to detach polymer from mucosa	Used to quantify adhesive strength experimentally

The evaluation of bioadhesion is an essential component of gastroretentive system development. In vitro methods commonly include mucin–polymer interaction studies, wash-off tests using excised gastric mucosa, and texture analyzer-based measurements of adhesive force. Ex vivo and in vivo studies provide more realistic insights into gastric retention and adhesion behavior under physiological conditions. These experimental approaches help correlate polymer properties and formulation variables with bioadhesive performance, enabling rational optimization of microsphere formulations [2, 4-6]. In conclusion, bioadhesion in gastroretentive mucoadhesive systems is governed by a complex interplay of physicochemical, mechanical, and biological factors. A thorough understanding of adhesion mechanisms and influencing parameters is essential for designing effective microsphere-based drug delivery systems capable of prolonged gastric retention and controlled drug release. The next section will focus on formulation strategies and optimization approaches used in the development of gastroretentive mucoadhesive microspheres, with particular emphasis on multifactorial design and evaluation methodologies [1, 35, 36, 72].

Formulation Strategies and Optimization of Gastroretentive Mucoadhesive Microspheres

The successful development of gastroretentive mucoadhesive microspheres requires a systematic formulation strategy that integrates polymer science, processing techniques, and optimization methodologies. Unlike conventional oral dosage forms, these systems are designed to achieve multiple objectives simultaneously, including prolonged gastric residence, strong mucoadhesion, optimal micromeritic properties, high drug encapsulation efficiency, and controlled drug release. Achieving this multifactorial performance necessitates careful selection of formulation components and process parameters, followed by rigorous optimization using scientifically sound experimental designs [9, 10, 57].

Various preparation techniques have been employed for the fabrication of gastroretentive mucoadhesive microspheres, with the choice of method largely depending on the physicochemical properties of the drug and polymers. Solvent evaporation and solvent diffusion methods are among the most widely used techniques due to their simplicity, scalability, and ability to produce uniform microspheres. In these methods, the drug and polymer are dissolved or dispersed in a suitable organic solvent and emulsified into an external phase containing a stabilizer, followed by solvent removal to form solid microspheres. Parameters such as polymer concentration, solvent type, stirring speed, emulsifier concentration, and phase volume ratio significantly influence particle size, surface morphology, and drug loading [2, 4-6].

Ionotropic gelation is another commonly employed technique, particularly for natural polymers such as alginate and chitosan. This method relies on the crosslinking of polymer chains in the presence of multivalent ions, resulting in the formation of gelled microspheres. Ionotropic gelation is advantageous due

to its mild processing conditions, absence of organic solvents, and suitability for thermolabile drugs. However, microspheres prepared using this technique may exhibit lower mechanical strength and faster drug release if crosslinking density is not adequately optimized [23, 24, 28, 60]. Spray drying and spray congealing techniques have also been explored for the preparation of mucoadhesive microspheres, especially when rapid processing and uniform particle size distribution are desired. These methods offer good reproducibility and scalability but may expose the formulation to thermal stress, which can be detrimental to heat-sensitive drugs or polymers. Emulsion crosslinking and phase separation methods further expand the range of formulation strategies available, allowing fine control over microsphere characteristics through adjustment of formulation and processing variables [25, 36].

Optimization of gastroretentive mucoadhesive microspheres involves balancing multiple interdependent variables to achieve the desired performance profile. Traditional one-factor-at-a-time approaches are often inefficient and fail to capture interactions between formulation variables. Consequently, modern formulation development increasingly relies on statistical design of experiments (DoE) to systematically study the effects of multiple factors and their interactions. Experimental designs such as factorial designs, Box–Behnken designs, and central composite designs are widely used to optimize polymer concentration, drug-to-polymer ratio, crosslinking agent concentration, stirring speed, and other critical parameters [23, 24, 28, 60].

The application of multifactorial optimization techniques enables the identification of critical formulation variables and their influence on key response parameters such as particle size, entrapment efficiency, mucoadhesive strength, and drug release rate. Response surface methodology provides graphical and mathematical tools to visualize the relationships between variables and responses, facilitating the selection of an optimized formulation with predictable performance. Such systematic optimization not only improves formulation robustness but also enhances reproducibility and scalability, which are essential for translational and industrial applications [27, 30, 37, 64].

Micromeritic properties are a critical consideration during formulation optimization, as they directly affect flow behaviour, packing efficiency, and dose uniformity. Parameters such as bulk density, tapped density, Carr’s index, Hausner ratio, and angle of repose are routinely evaluated to assess flow characteristics. Optimized microspheres should exhibit good to excellent flow properties to ensure uniform filling during capsule or tablet manufacturing. Particle size distribution also plays a crucial role in gastric retention and drug release; smaller particles may exhibit faster drug release but reduced retention, whereas excessively large particles may compromise patient acceptability and uniform distribution within the stomach.

Mucoadhesive strength is another key response variable that must be carefully optimized. Excessive adhesion may lead to localized accumulation of microspheres and potential mucosal irritation, whereas insufficient adhesion may result in premature gastric emptying. In vitro and ex vivo bioadhesion studies are therefore integral to the optimization process, providing quantitative measures of adhesive performance. The choice and ratio of polymers, degree of crosslinking, and surface characteristics of microspheres are adjusted to achieve an optimal balance between adhesion and release behaviour [51, 54, 65, 67, 68].

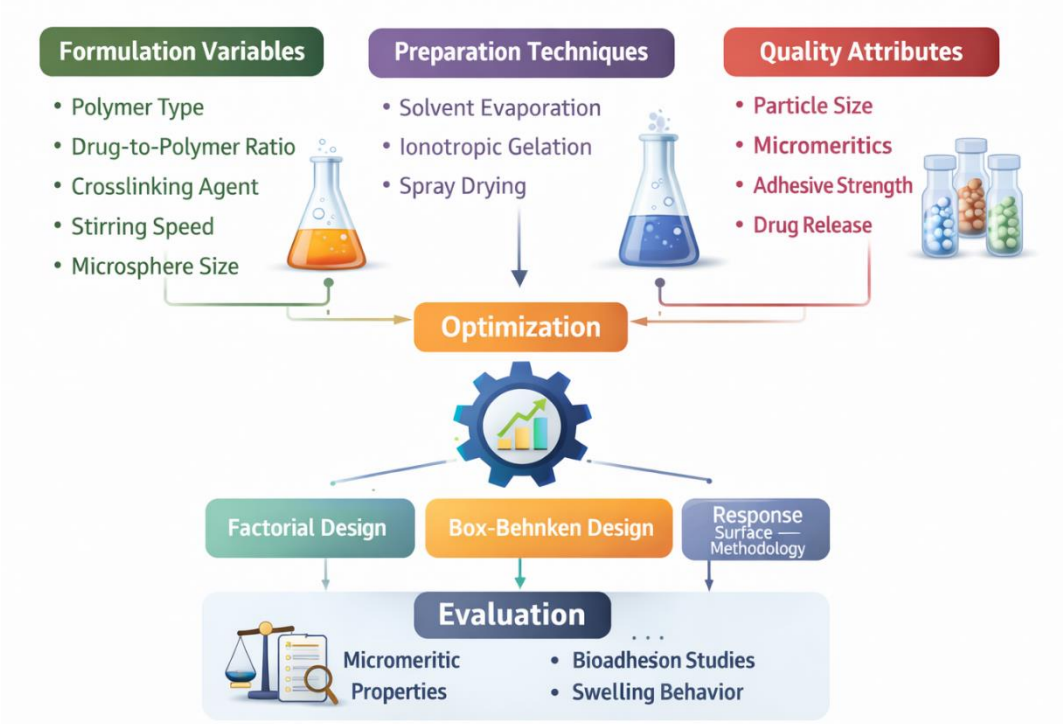

Figure 3. Multifactorial formulation and optimization strategy for gastroretentive mucoadhesive microspheres, illustrating the interaction between formulation variables and performance outcomes.

Drug release modulation represents a central objective of formulation optimization. By varying polymer composition, matrix density, and microsphere size, it is possible to tailor release profiles ranging from sustained to controlled release over extended periods. In vitro drug release studies conducted in simulated gastric fluid provide insights into release kinetics and mechanisms. Mathematical modeling of release data helps identify whether diffusion, erosion, or a combination of mechanisms governs drug release, thereby guiding further formulation refinement [51, 54, 65, 67, 68].

Table 3. Key formulation variables and their influence on critical quality attributes of gastroretentive mucoadhesive microspheres.

Formulation Variable	**Effect on Microsphere Characteristics**	**Impact on Performance**
Polymer type	Determines swelling, adhesion, and release behavior	Controls gastric retention and bioadhesive strength
Drug-to-polymer ratio	Influences encapsulation efficiency and release rate	Higher polymer content slows drug release
Polymer concentration	Affects particle size and matrix density	Improves sustained release but may reduce diffusion
Crosslinking agent concentration	Controls rigidity and porosity	Excess crosslinking may reduce drug release
Stirring speed	Influences particle size and uniformity	Higher speed produces smaller microspheres
Preparation method	Determines morphology and encapsulation	Affects reproducibility and scalability
Microsphere size	Governs surface area and release kinetics	Smaller particles show faster release
Swelling behavior	Controls adhesion and diffusion	Optimal swelling enhances retention and release control

In summary, formulation strategies for gastroretentive mucoadhesive microspheres require a holistic and systematic approach that integrates material selection, preparation techniques, and multifactorial optimization. The use of advanced experimental designs and response surface methodologies enables

precise control over formulation attributes, resulting in microspheres with predictable gastric retention, strong mucoadhesion, and controlled drug release. The final section of this review will discuss evaluation parameters, in vitro release behaviour, and future perspectives in the development of gastroretentive mucoadhesive drug delivery systems.

Evaluation Parameters, In Vitro Release Behaviour, and Future Perspectives

Comprehensive evaluation of gastroretentive mucoadhesive drug delivery systems is essential to establish their pharmaceutical quality, functional performance, and therapeutic potential. Evaluation parameters are designed to assess not only the physical integrity and uniformity of microspheres but also their ability to adhere to the gastric mucosa, remain in the stomach for extended periods, and deliver the drug in a controlled and predictable manner. These assessments collectively provide critical insights into formulation robustness and guide further optimization [37, 63, 64]. Physicochemical evaluation begins with the assessment of particle morphology, surface characteristics, and size distribution. Scanning electron microscopy is commonly employed to examine microsphere shape, surface smoothness, and porosity, which can influence both mucoadhesion and drug release behavior. Uniform, spherical microspheres with smooth or moderately rough surfaces are generally preferred, as they ensure consistent flow properties and reproducible release profiles. Particle size analysis, typically performed using optical microscopy or laser diffraction techniques, provides information on size distribution, which plays a crucial role in gastric retention and release kinetics [51, 54, 65, 67, 68].

Micromeritic evaluation remains a cornerstone of quality assessment for multiparticulate systems. Bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose are routinely measured to evaluate flowability and packing behavior. Good flow properties are essential for downstream processing, particularly during capsule filling or tablet compression. Microspheres exhibiting poor flow may lead to weight variation and dose inconsistency, underscoring the importance of optimizing these parameters during formulation development.

Drug content uniformity and encapsulation efficiency are critical indicators of formulation reliability and therapeutic consistency. High encapsulation efficiency reflects effective drug entrapment within the polymer matrix and minimizes drug loss during processing. Uniform drug distribution ensures consistent dosing and predictable pharmacokinetic behaviour. These parameters are typically evaluated using validated analytical techniques such as UV–visible spectrophotometry or high-performance liquid chromatography, depending on the drug's analytical characteristics [37, 63, 64].

Mucoadhesive performance is evaluated using a combination of in vitro and ex vivo techniques. In vitro wash-off studies using excised gastric mucosa provide a simple and reproducible method for assessing adhesive strength and retention under simulated gastric conditions. Texture analyzer-based methods offer quantitative measurement of detachment force, enabling comparison of different formulations and polymer combinations. Ex vivo studies using animal gastric tissue provide more physiologically relevant insights into adhesive behaviour and help bridge the gap between in vitro findings and in vivo performance. Swelling behaviour is another important evaluation parameter, as it directly influences both mucoadhesion and drug release. Swelling index studies conducted in simulated gastric fluid provide information on polymer hydration, matrix expansion, and structural stability. An optimal swelling profile enhances adhesion by increasing contact area with the mucosa while maintaining matrix integrity to prevent premature drug release or erosion [30, 32, 62, 65].

In vitro drug release studies are central to the evaluation of gastroretentive mucoadhesive microspheres. These studies are typically performed in simulated gastric fluid under controlled conditions to mimic the acidic environment of the stomach. Release profiles provide insights into the rate and extent of drug release over time and help determine whether the formulation achieves the desired sustained or controlled release behavior. Mathematical modeling of release data using kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations enables elucidation of the underlying release mechanisms. Such analyses aid in correlating polymer properties and formulation variables with drug release behaviour [51, 66]. While in vitro evaluations provide valuable preliminary data, in vivo studies are ultimately required to confirm gastric retention, bioadhesive performance, and therapeutic efficacy. Imaging

techniques such as gamma scintigraphy and radiographic methods have been used to visualize gastric retention and transit behavior of microsphere formulations. Pharmacokinetic studies further validate the ability of gastroretentive systems to enhance bioavailability, prolong plasma drug levels, and reduce dosing frequency. However, ethical considerations, cost, and experimental complexity often limit extensive in vivo investigations during early development stages [30, 32, 62, 65].

Despite significant progress, several challenges remain in the development and translation of gastroretentive mucoadhesive drug delivery systems. Variability in gastric physiology, mucus turnover, and feeding conditions can lead to inter- and intra-subject differences in formulation performance. Additionally, long-term safety of prolonged mucosal adhesion, particularly with high polymer loads, requires careful evaluation. Manufacturing scalability, batch-to-batch consistency, and regulatory acceptance also pose challenges, especially for complex multiparticulate systems involving multiple polymers and processing steps [1, 72]. Future research in this field is expected to focus on the development of smart and stimuli-responsive mucoadhesive systems capable of adapting to dynamic gastric conditions. Advances in polymer chemistry, including the synthesis of novel bioadhesive polymers and polymer blends, are likely to enhance adhesion strength and release control while minimizing variability. The integration of quality by design principles and advanced modeling techniques will further improve formulation predictability and robustness. Additionally, the incorporation of biorelevant in vitro testing models may improve the correlation between in vitro and in vivo performance, accelerating formulation development and regulatory approval [1, 72].

In conclusion, oral gastroretentive mucoadhesive drug delivery systems represent a promising and versatile approach for improving the therapeutic performance of orally administered drugs. The strategic use of polymeric carriers, informed by a thorough understanding of bioadhesion mechanisms and release modulation strategies, enables the development of robust and effective microsphere-based formulations. Continued advancements in formulation science, evaluation methodologies, and polymer technology are expected to further expand the clinical applicability and commercial viability of these systems.

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