EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Coden USA: EJBPBO
Volume: 13
Issue: 5
Year: 2026

DESIGN AND CHARACTERIZATION OF ORAL MUCOADHESIVE MICROSPHERES: A REVIEW

Indra Kumar Dubey*[1], Swatantra Kumar Singh Kushwaha[2], Diptee Gupta[2]

*[1]Research Scholar, Krishna Institute of Pharmacy and Sciences, Kanpur-209217, India.
[2]Krishna Institute of Pharmacy and Sciences, Kanpur-209217, India.

***Corresponding Author: Indra Kumar Dubey**
Research Scholar, Krishna Institute of Pharmacy and Sciences, Kanpur-209217, India.

DOI: https://doi.org/10.5281/zenodo.20133047

How to cite this Article: Indra Kumar Dubey*[1], Swantra Kumar Singh Kushwaha[2], Diptee Gupta[2]. (2026). Design and Characterization of Oral Mucoadhesive Microspheres: A Review. European Journal of Biomedical and Pharmaceutical Sciences, 13(5), 371–380.
This work is licensed under Creative Commons Attribution 4.0 International license.

Article Received on 15/04/2026 **Article Revised on 05/05/2026** **Article Published on 10/05/2026**

ABSTRACT
The present work aims to discuss the design and characterization of oral mucoadhesive microspheres. Oral mucoadhesive microspheres represent a sophisticated drug delivery system engineered to enhance the bioavailability of therapeutic agents through prolonged residence time at the absorption site. This review aims to systematically analyze the design principles, material selection, and characterization techniques critical for developing effective oral mucoadhesive microspheres. Specifically, it will delve into the nuanced interplay between polymer properties, fabrication methodologies, and their subsequent impact on mucoadhesion mechanisms and drug release kinetics. A comprehensive understanding of these aspects is crucial for the rational design and successful development of next-generation oral mucoadhesive microspheres. This comprehensive review will therefore serve as a critical resource for researchers and pharmaceutical scientists engaged in the development of innovative oral drug delivery platforms. It will synthesize current knowledge on the factors governing mucoadhesion, including surface charge, polymer chain entanglement, and hydration dynamics, alongside their quantitative assessment methods. It will also critically evaluate the various in vitro and in vivo models employed for assessing mucoadhesion strength and drug release profiles, highlighting their respective strengths and limitations.

KEYWORDS: Mucoadhesion, Mucoadhesive Microspheres, Bioavailability, Alginates, Carbopol, Chitosan.

INTRODUCTION
Mucoadhesive microspheres serve as a sophisticated oral controlled-release mechanism designed to extend the duration a drug remains at its intended site of absorption. By adhering to the mucosal lining upon hydration, these systems effectively localize medication within the gastrointestinal tract (GIT) for extended periods. This localization is critical for maintaining consistent, therapeutic plasma drug levels, which significantly reduces the need for frequent dosing and prevents the erratic peaks and valleys often seen in steady-state drug concentrations. (Raj, Mucoadhesive microspheres: A targeted drug delivery system., 2021) Microspheres are a cornerstone of modern drug delivery, valued for their compact size and exceptional ability to transport therapeutic agents. By integrating bioadhesive properties into these carriers, researchers can overcome the challenge of rapid transit times, creating mucoadhesive microspheres that remain in place longer. This concept relies on bioadhesion, which is the mechanism by which two materials—where at least one is a biological substance—are securely bonded together over an extended duration through interfacial forces. (Gopaiah, Formulation and characterization of mucoadhesive microspheres of aceclofenac., 2022)

Microspheres are specialized carrier-based delivery systems consisting of a medicinal core encased within a protective polymer shell, typically ranging in size from 1 to 1000 me. These systems are designed to improve drug stability and release.

The concept of bioadhesion refers to the ability of these polymeric materials to stick to biological surfaces; specifically, when this attachment occurs on mucosal membranes, the process is precisely termed

mucoadhesion. (Gopaiah, Formulation and characterization of mucoadhesive microspheres of aceclofenac, 2022) Broadly defined, bioadhesion is the formation of a bond between two biological entities or between a biological surface and a synthetic material. Within the context of pharmaceutical delivery, this term specifically describes the attachment of natural or synthetic polymers to soft tissues or the mucosal lining of the gastrointestinal tract. When this connection specifically involves the mucus layer, mucoadhesion is often used interchangeably with bioadhesion to describe the phenomenon. (Pandey J. S., 2020)

Advantages of Mucoadhesive Microsphere

- Sustained Therapeutic Impact: They ensure a steady drug release, providing a prolonged medicinal effect.
- Enhanced Patient Adherence: By decreasing the required daily dosage frequency, these systems make treatment regimens easier for patients to follow.
- Optimized Bioavailability: Improved drug absorption leads to higher efficacy while simultaneously lowering the risk of systemic side effects. (Ganju, 2024)
- Tailored Release Profiles: The specific physical structure and morphology of the spheres allow for precise control over how the polymer degrades and how the medication is liberated.
- Tunable Disintegration: The spherical design provides flexibility in managing both the breakdown of the carrier and the timing of drug delivery.

Limitations of Mucoadhesive Microsphere

- Consistency Challenges: Maintaining a uniform release profile across different batches or formulations can be difficult. (Ganju, 2024)
- Physiological Interference: External factors—including a patient's diet, gastric transit speed, and the natural turnover rate of the mucus layer—can unpredictably alter the drug release rate.
- Dose-Dependent Variability: The speed at which the drug is released may fluctuate significantly between different dosage strengths. (Ganju, 2024)
- Risk of Toxicity: If the integrity of the controlled-release mechanism is compromised (e.g., "dose dumping"), it could lead to dangerously high concentrations and toxic effects.
- Administration Restrictions: These dosage forms must be swallowed whole; they cannot be crushed or chewed without destroying their specialized release properties.

Bioadhesion

Bioadhesion is defined as the persistent attachment of two surfaces—where at least one is biological—via interfacial forces. When this interaction specifically involves a polymer adhering to a mucosal membrane, the process is specialized as mucoadhesion. (Pawar, 2024)

Mucus membranes

Mucus membranes are the moist linings found throughout various internal tracts, such as the respiratory and gastrointestinal systems. These surfaces are continuously lubricated by mucus, which is secreted by specialized cells. This substance exists in three primary states: a gel layer that adheres directly to the membrane, suspended mucus, and soluble mucus found within the lumen. (Dewangan, Mucoadhesive microspheres of atorvastatin calcium: rational design, evaluation and enhancement of bioavailability, 2021)

Chemically, mucus is a complex mixture primarily composed of mucin glycoproteins, water, inorganic salts, and lipids. Beyond its role as a lubricant to ease transit, it serves as a critical biological barrier, protecting the underlying tissues from environmental and chemical threats. (Chechare, Formulation and evaluation of mucoadhesive microspheres of metronidazole., 2024)

Mechanism Of Mucoadhesion

The mechanism of mucoadhesion is a complex, multi-step process that facilitates the attachment of a delivery system to a mucosal surface. It is generally understood through a two-phase process: the Contact Stage and the Consolidation Stage as shown in Figure 1. (Beg, Nasal mucoadhesive microspheres of lercanidipine with improved systemic bioavailability and antihypertensive activity., 2021)

Phase 1: The Contact Stage

This initial stage involves the physical approach and wetting of the polymer

- Wetting and Swelling: When the microsphere reaches the mucous membrane, the polymer absorbs water from the mucus gel. This causes the microsphere to swell, making it flexible and increasing the surface area available for interaction.

- **Intimate Contact:** The hydrated polymer spreads over the mucus surface, overcoming any surface tension to establish a close physical connection. (Alawdi, 2021)

Phase 2: The Consolidation Stage

This stage involves the chemical and physical "locking" of the two surfaces to ensure a long-lasting bond.

- **Interpenetration:** The long, chain-like molecules of the polymer and the mucin glycoproteins begin to move and physically "weave" into one another. Imagine this as two brushes being pushed together so the bristles interlock.
- **Chemical Bonding:** Once the chains are entangled, several types of secondary chemical bonds form to strengthen the attachment
- **Hydrogen Bonding:** Occurs between hydrophilic groups (like $-OH$ or $-COOH$).
- **Electrostatic Attraction:** Occurs between positively charged polymers (e.g., Chitosan) and negatively charged mucin.

- **Van der Waals Forces:** Weak, short-range physical attractions.
- **Hydrophobic Interactions:** Forces between non-polar regions of the molecules. (Mamatha, A review on: mucoadhesive drug delivery systems., 2022.

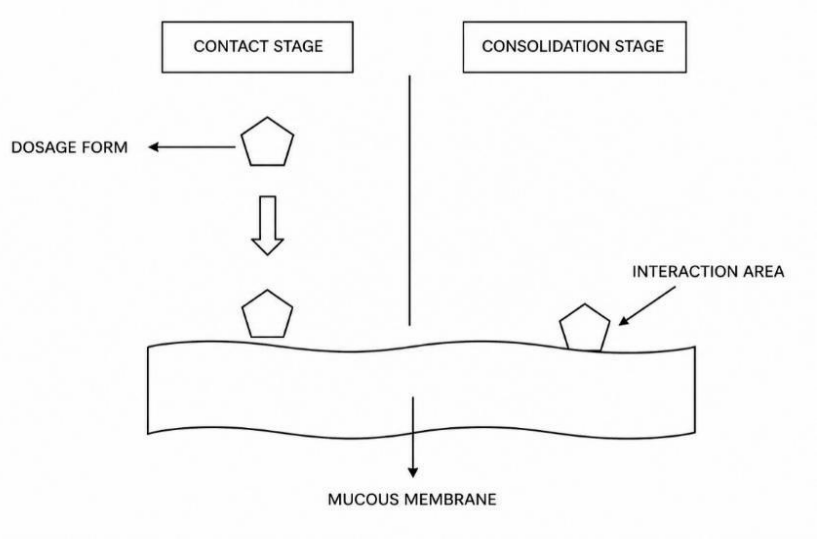

Figure 1: Mechanism of Mucoadhesion.

Theories of Mucoadhesion

There are several general theories that can explain mucoadhesion such as electronic theory, adsorption theory, wetting theory, diffusion theory, fraction theory and mechanical theory. For an overview, the theories explained by different researchers are summarized-

1. The Electronic Theory

This theory proposes that mucoadhesion is driven by **electrostatic forces**. It suggests that when a polymer makes contact with the mucus, a transfer of electrons occurs between the two surfaces. This creates an **electrical double layer** at the interface, resulting in an attractive force similar to a capacitor. (Mamatha, A review on: mucoadhesive drug delivery systems., 2022)

2. The Adsorption Theory

This is the most widely accepted perspective. it suggests that adhesion is the result of secondary **intermolecular forces**. These include:

- **Hydrogen bonding:** The most common bond in mucoadhesive polymers.
- **Van der Waals forces:** Weak, short-range physical attractions.
- **Hydrophobic interactions:** Attraction between non-polar regions. (Stankovits, 2025)

3. The Wetting Theory

Commonly applied to liquid or low-viscosity systems, this theory focuses on the **spread ability** of the drug carrier. It posits that the lower the contact angle between the adhesive and the mucosal surface, the higher the affinity and bond strength. High "wettability" ensures the polymer can flow into every fold of the tissue. (Desai, 2025)

4. The Diffusion Theory

This theory emphasizes **physical entanglement**. It suggests that the long, flexible polymer chains from the drug carrier physically migrate and "interweave" with the glycoprotein (mucin) strands of the mucus. This creates a semi-permanent, three-dimensional network that anchors the device in place. (Sun, 2022)

5. Fracture Theory

According to this theory, the strength of mucoadhesion is measured by the fracture strength- the maximum stress required to separate the delivery system from the mucosal surface. It assumes that the bond will eventually fail at its weakest point, which is usually either:

1. **The Interface:** Where the polymer meets the mucus.
2. **The Cohesive Layer:** Within the mucus itself or within the polymer gel. (Chauhan, 2022)

6. The Mechanical Theory

This describes a "lock and key" physical mechanism. It proposes that mucoadhesion occurs when a liquid or semi-solid adhesive flows into the **micro-cracks, pores, and irregularities** of the mucosal surface as in figure 2. Once the material settles or solidifies within these gaps, it forms a mechanical interlocking structure that resists detachment. It describes how mucoadhesion occurs, which is the consequence of liquid adhesives diffusing into the microcracks and imperfections of the mucoadhesive substrate, and how this forms an interlocking structure. (Subramanian, 2021)

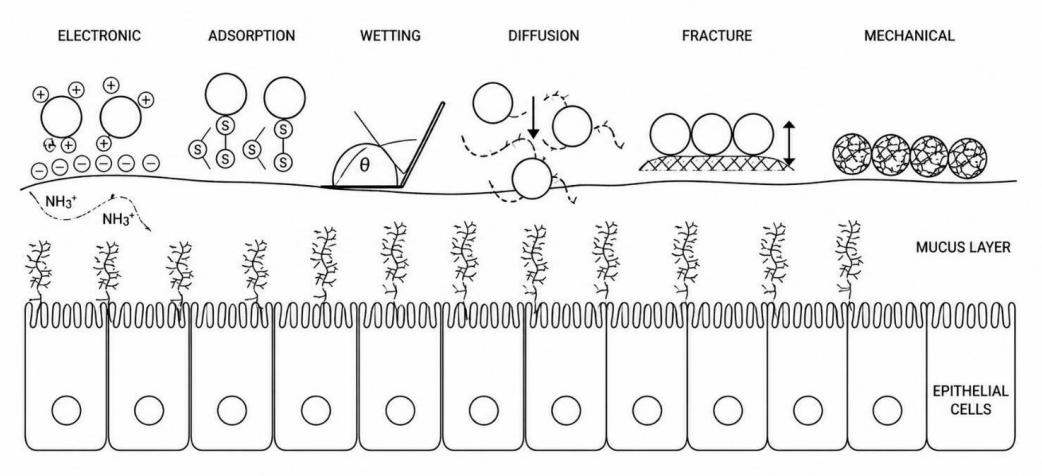

Figure 2: The Mechanical Theory diagram.

Polymers used in Mucoadhesive Drug delivery system

A vast array of polymers has been utilized in the development of Mucoadhesive Drug Delivery Systems (MDDS), typically classified by their ionic charge into cationic, anionic, non-ionic, and thiolated categories. Among these, chemical groups such as acrylates (e.g., Carbopol), cellulose derivatives (e.g., HPMC), chitosan, and alginates are the most widely researched and utilized. Furthermore, contemporary designs often incorporate composite materials, chemically tailored polymers, or synergistic polymer blends to optimize the performance and efficiency of the delivery system. (Raj, Mucoadhesive microspheres: A targeted drug delivery system., 2021)

1. Cellulose Derivative

Cellulose-based derivatives are classified as "first-generation" mucoadhesive polymers and remain among the most frequently utilized materials in drug delivery. Key examples include hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), and carboxymethyl cellulose (CMC).

These polymers are favored for their biocompatibility and their ability to form a viscous, adhesive gel upon contact with water, making them ideal candidates for extending the residence time of medications on mucosal surfaces. (Bader, 2013)

The adhesive process is driven by the development of **hydrogen bonds** between the carboxylic acid functional groups of cellulose-based polymers and the mucin glycoproteins. The intensity of this connection is directly proportional to the strength of these hydrogen bonds; more robust bonding results in deeper penetration and a firmer attachment to the mucosal surface. (Baloğlu E, 2010)

2. Chitosan

Ranking as the most abundant natural polysaccharide after cellulose, chitosan has been the subject of intensive scientific investigation since the early 1980s. This cationic mucoadhesive is a copolymer of glucosamine and N-acetyl-glucosamine, synthesized via the deacetylation of chitin. Although it is insoluble in water, it effectively dissolves in dilute weak acids; its widespread use as a polymeric component is largely due to its favorable biocompatibility, biodegradability, and low toxicity. Chitosan's mucoadhesive properties arise from several factors, most notably the formation of hydrogen bonds between its hydroxyl and amino groups and the glycoproteins in mucin, as well as the structural flexibility of its linear molecules which facilitates surface attachment. (Ahmad, 2024)

Chitosan is used for successful development of the different mucoadhesive delivery system. However, the oral delivery with chitosan containing devices is not very popular because at higher pH (6-6.5) chitosan precipitates. So, in the distant region of the gastrointestinal tract chitosan may lose its mucoadhesive and permeation enhancing property. (Singh S. C., 2023)

3. Alginates

Derived from brown seaweed, alginate is a natural, biodegradable anionic polymer that has become a staple in scientific research due to its cost-effectiveness and favorable safety profile. Because of its low toxicity, it is frequently utilized in the development of microparticles and beads, both of which are prized for their superior bioadhesive characteristics. (Raj, Mucoadhesive microspheres: A targeted drug delivery system, 2021)

In acidic environments, alginate exhibits limited swelling, which causes the polymeric chains to remain tightly coiled. This state hinders the chains from uncoiling and entangling with the mucus layer—a process necessary for strong attachment. Consequently, the mucoadhesive effectiveness of alginate is significantly reduced at a low pH compared to more neutral conditions. (Ainurofiq, 2023)

Researchers in the pharmaceutical field frequently combine alginate with various other bioadhesive carriers to engineer advanced drug delivery systems. A notable application of this strategy is the development of

chitosan-alginate beads, which are utilized for the vaginal administration of chlorhexidine digluconate to leverage the synergistic properties of both polymers. (Pathak, 2020)

The mucoadhesive strength of alginate is fundamentally dictated by its molecular weight. Research indicates that low molecular weight alginate chains are relatively rigid, which limits their ability to bridge and interpenetrate with mucin molecules. In contrast, high molecular weight alginate possesses greater flexibility, allowing for superior entanglement with the mucus layer and resulting in significantly stronger bioadhesion. (Kulkarni, 2023)

4. Carbopol

Carbopol is a versatile family of high-molecular-weight, synthetic polymers primarily composed of cross-linked acrylic acid chains. In its dry, powdered form, the polymer exists as tightly coiled molecules, but once dispersed in an aqueous medium, these chains begin to hydrate and partially unroll. The defining characteristic of Carbopol is its transition upon neutralization; by adding a basic substance to increase the pH, the acidic carboxyl groups along the polymer backbone ionize and acquire a negative charge. This creates an electrostatic repulsion that forces the polymer to swell extensively, trapping water and transforming a liquid into a structured, high-viscosity gel or a stable emulsion. (Hamdi, 2023)

Beyond its thickening capabilities, Carbopol is highly valued in the pharmaceutical and cosmetic sectors for its rheological properties, specifically its "shear-thinning" behavior. This allows a product to remain thick and suspended while at rest—preventing ingredients from settling—yet flow easily when pumped or spread on the skin. Unlike many natural gums, Carbopol provides exceptional clarity, making it the industry standard for transparent products like hand sanitizers and hair styling gels. However, the integrity of its gel network is notably sensitive to the presence of electrolytes; high concentrations of salts can shield the ionic charges on the polymer backbone, causing the structure to collapse and significantly reducing the viscosity of the formulation. (Safitri, 2021)

Methodologies used in preparation of mucoadhesive microspheres

1. Solvent evaporation

As the most frequently utilized microencapsulation technique—initially pioneered by Ogawa and his team—this process begins by preparing an aqueous drug solution, either buffered or plain, which typically includes a viscosity-enhancing or stabilizing agent. This internal water phase is introduced into an organic polymer solution and stirred continuously to create a primary water-in-oil (w/o) emulsion. (Raj, Mucoadhesive microspheres: A targeted drug delivery system, 2021)

To form the final structure, this primary emulsion is dispersed into a larger volume of water containing emulsifying agents such as polyvinyl alcohol (PVA) or polyvinyl pyrrolidone (PVP), resulting in a multiple water-in-oil-in-water (w/o/w) emulsion. The system is then stirred steadily to facilitate the evaporation of the organic solvent, which causes the polymer to precipitate and harden into solid microspheres. Finally, these particles are recovered through washing and centrifugation before being lyophilized (freeze-dried) to produce a stable, free-flowing powder shown in figure 3. (Chechare, Formulation and evaluation of mucoadhesive microspheres of metronidazole., 2024)

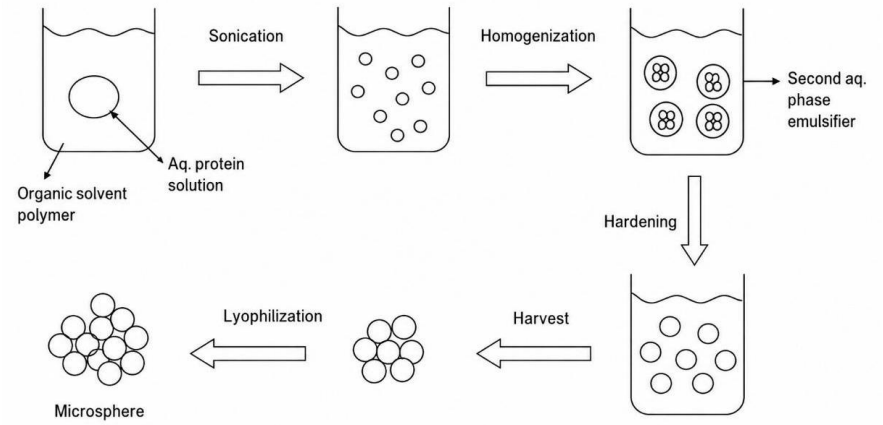

Figure 3: Solvent Evaporation method for preparation of mucoadhesive microspheres.

2. Spray Drying

This microencapsulation strategy relies on the rapid dehydration of atomized droplets within a continuous flow of heated air. The process begins by dissolving the polymer in an aqueous medium, followed by the incorporation of the drug—either through dissolution or dispersion—along with a compatible cross-linking agent. When this mixture is atomized into the hot air stream, it produces dry, free-flowing microparticles shown in figure 4. (Bhalala, 2026)

To refine the morphology of the spheres, plasticizers like citric acid can be introduced; these additives encourage polymer coalescence, resulting in a smoother and more

uniform surface finish. A significant advantage of this technique is its versatility, as it is relatively unaffected by the specific solubility of the drug or polymer. Furthermore, the final particle size can be precisely tuned by adjusting operational variables such as the spray rate, feed velocity, nozzle diameter, and drying temperature. Because of its simplicity and high reproducibility, this method is exceptionally well-suited for industrial scale-up. (Kakkar, 2020)

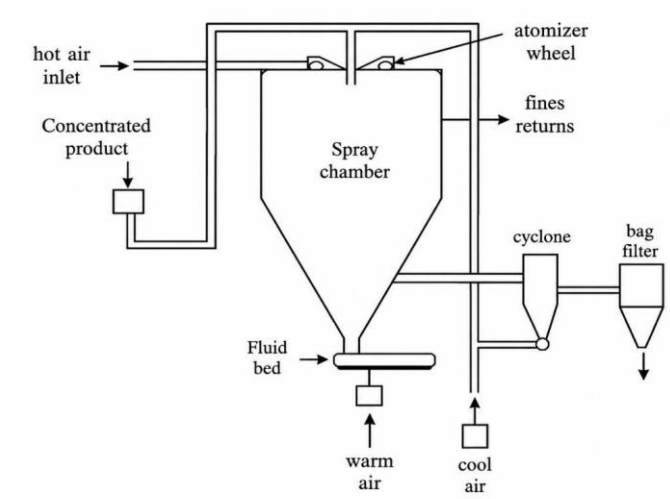

Figure 4: Spray Dring method for preparation of mucoadhesive microspheres.

3. Phase Inversion Method

This technique centers on introducing the drug into a dilute polymer solution using methylene chloride as the primary solvent. The resulting mixture is then poured into a significantly larger volume (1:100 ratio) of a powerful non-solvent, such as petroleum ether, within an unstirred bath. Upon contact with the non-solvent, the polymer precipitates to form microspheres. These microparticles are subsequently recovered through clarification, purified with a petroleum ether wash, and allowed to air dry to reach their final state shown in figure 5. (Pattanayak, Preparation and Evaluation of Ketoprofen Loaded Mucoadhesive Microspheres., 2024)

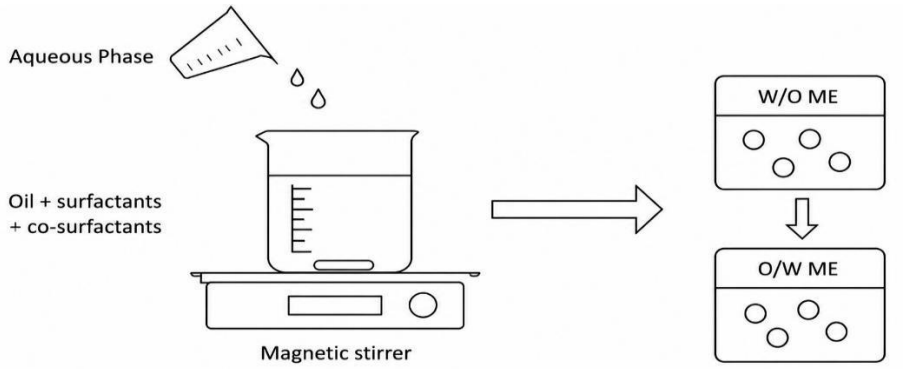

Figure 5: Phase inversion method for preparation of mucoadhesive microspheres.

4. Hot Melt Microencapsulation

The initial synthesis of polyanhydride copolymer microspheres—specifically poly bis(p-carboxyphenoxy) propane anhydride combined with sebacic acid—was achieved through this particular technique. (Pandey J. S., Development of nasal mucoadhesive microspheres of granisetron: A potential drug., 2020)

The process begins by melting the polymer, followed by the integration of solid drug particles through constant agitation. This medicinal mixture is then dispersed into an immiscible medium, such as silicone oil, while being stirred and heated beyond the polymer's melting threshold to create a stable emulsion. To finalize the structure, the emulsion is cooled until the polymer droplets solidify into particles. These microspheres are then isolated via filtration and purified through a petroleum ether wash. (Gurung, 2020)

5. Complex Coacervation

This method is fundamentally based on the separation of a liquid precipitate that occurs when two hydrophilic colloid solutions are mixed under specific conditions. The process involves dissolving an immiscible polymer into a

suitable vehicle to create the coating phase, into which the core material is then dispersed using continuous agitation shown in figure 6. (Singh I. D., 2021)

The actual encapsulation is triggered through phase separation, which can be induced by several variables:

- Thermal shifts: Altering the temperature of the polymer solution.
- Chemical adjustments: Changing the pH or adding salts.
- Solubility changes: Introducing a non-solvent or an incompatible polymer.
- Molecular interaction: Inducing polymer-polymer interactions.

To complete the process, the coating is solidified through desolvation or thermal cross-linking, resulting in a durable, self-sustaining microsphere. (Beg,. Nasal mucoadhesive microspheres of lercanidipine with improved systemic bioavailability and antihypertensive activity., 2021)

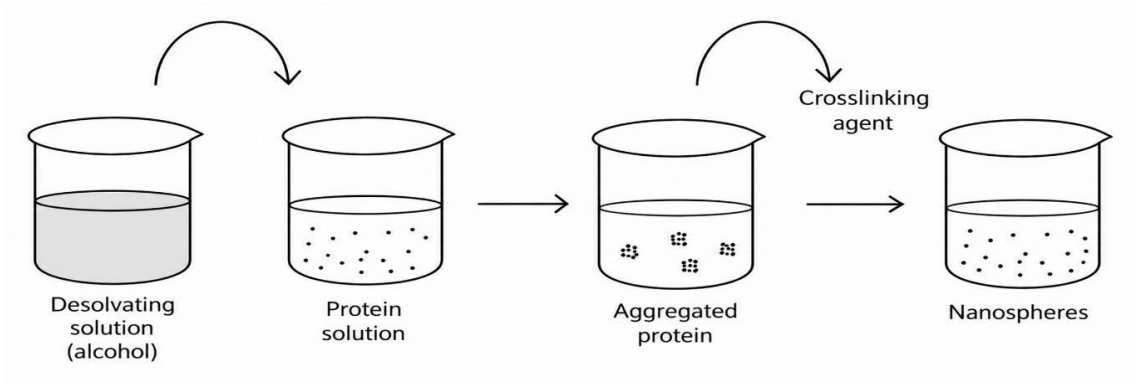

Figure 6: Coacervation Process.

6. Single Emulsion Technique

The production of natural polymer microspheres frequently utilizes the single emulsion technique. This process begins by dissolving or dispersing the drug and polymer within an aqueous medium, which is subsequently introduced into an organic phase, such as oil as shown in figure 7. Through continuous agitation, the mixture forms discrete droplets or globules. To transform these droplets into rigid structures, the dispersed phase is subjected to cross-linking, which can be achieved through either thermal application or the introduction of chemical cross-linkers like glutaraldehyde, formaldehyde, or diacid chloride. This hardening step ensures the creation of stable, solid microspheres suitable for drug delivery. (Deshmukh, 2023)

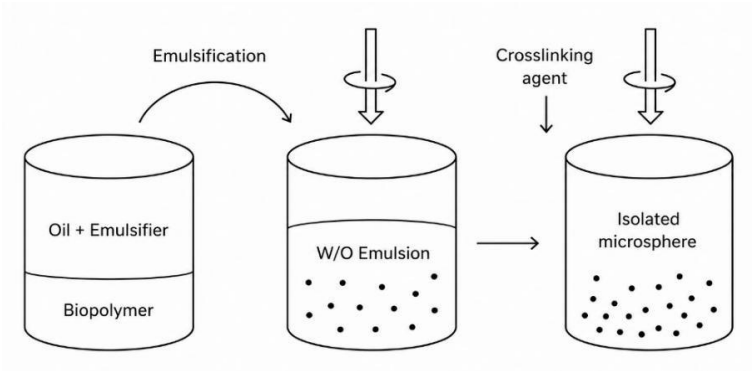

Figure 7: Single Emulsion Technique.

7. Double Emulsion Method

Developed by Ogawa et al. in 1988, this technique remains the most prevalent approach for microencapsulation. The process begins by blending an aqueous drug-polymer solution into an organic phase under high-speed agitation to create a primary water-in-oil (w/o) emulsion. (Sahu, 2020)

This initial mixture is then introduced into a larger volume of water supplemented with an emulsifying agent—such as polyvinyl alcohol or polyvinylpyrrolidone—while maintaining constant stirring. This creates a secondary water-in-oil-in-water (w/o/w) multiple emulsion. As stirring persists, the organic solvent gradually evaporates, resulting in the formation of hardened microspheres, which are subsequently rinsed and dried for final use. (Khan, 2020)

Evaluation of Mucoadhesive Microsphere

There are the following parameters for the evaluation of

mucoadhesive microsphere-

1. Particle Size and Shape

Both light microscopy (LM) and scanning electron microscopy (SEM) are effective analytical tools for evaluating the physical characteristics of microspheres, specifically their dimensions, morphology, and surface topography. (Chechare, Formulation and evaluation of mucoadhesive microspheres of metronidazole., 2024)

2. Surface charge study

Using photon correlation spectroscopy, the surface charge—or zeta potential—of mucoadhesive microspheres is calculated by translating measured electrophoretic mobility through integrated software, which applies the Helmholtz–Smoluchowski equation. This measurement serves as a vital indicator of the particles' surface charge, allowing researchers to predict and regulate the microspheres' stability, adhesive strength, and specific mucoadhesive mechanisms. Because the mucoadhesion process relies on structural and electrical interactions between polymers and the mucus layer, determining the zeta potential for both components is essential for forecasting the electrostatic forces that drive their bond. (Pandey J. S., Development of nasal mucoadhesive microspheres of granisetron: A potential drug, 2020)

3. Entrapment Efficiency

The entrapment efficiency (EE), or percent entrapment,

$$Percent\ swelling\ = \frac{D_T\ - D_0}{D_0 \times 100}$$

Where

- DO represents the initial weight of the dried microspheres.
- DT represents the weight of the swelled microspheres after fluid absorption.

5. Surface Characterization

Surface morphology and the structural evolution of microspheres during polymer degradation are primarily analyzed using scanning electron microscopy (SEM), scanning tunneling microscopy (STM), and general electron microscopy (EM). (Mady, 2021)

To observe these morphological transitions, microspheres are typically incubated in phosphate-buffered saline (PBS), with samples retrieved and examined at specific time intervals to track the degradation process. Research indicates that surface texture significantly influences performance; microspheres with a coarser surface facilitate stronger mechanical interlocking, thereby enhancing mucoadhesive strength. Conversely, microspheres with a smooth surface generally exhibit weaker mucoadhesive properties due to reduced physical interaction with the target tissue. (Pattanayak, Preparation and Evaluation of Ketoprofen Loaded Mucoadhesive Microspheres, 2024)

is determined by lysing the microspheres in a buffer solution to release the encapsulated drug. Once the spheres are fully broken down, the resulting lysate is filtered or centrifuged, and the concentration of the active pharmaceutical ingredient is measured according to standard monograph procedures. (Sangeeta, 2023)

The percentage of entrapment is then calculated by comparing the amount of drug actually recovered to the amount originally intended to be encapsulated, using the following formula:

$$\% \text{ Entrapment} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

4. Swelling Index

The swelling index measures the capacity of mucoadhesive microspheres to absorb fluids at the site of administration. This expansion is a critical first step, as the hydration and subsequent swelling of the polymer chains are necessary to initiate the process of mucoadhesion. (Dewangan, Dewangan, H. K., Sharma Mucoadhesive microspheres of atorvastatin calcium: rational design, evaluation and enhancement of bioavailability, 2021)

To quantify this, the percentage of swelling is calculated by comparing the mass of the hydrated microspheres to their initial dry state using the following equation:

6. Bulk Density

To determine the bulk density (often specifically the tapped density in this context), the fabricated microspheres are weighed and placed into a 10-ml graduated glass cylinder. The cylinder is subjected to mechanical tapping using an automated device until the volume of the microsphere bed reaches a stable, constant state. The density is then calculated as the ratio of the microspheres' mass to the final volume occupied by the tapped bed. (Jamkar, 2020)

7. Angle of Contact

The contact angle is measured to evaluate the wetting characteristics of micro-particulate carriers, providing a clear indication of whether the microspheres are hydrophilic or hydrophobic. As a specific thermodynamic property of the solid, this measurement is sensitive to any adsorbed components on the surface. (Noreen, 2023)

The analysis is conducted at the solid/air/water interface. To determine the advancing and receding contact angles, a droplet is placed within a circular cell positioned above the objective of an inverted microscope. These measurements are typically recorded at 20°C within one minute of the microspheres being deposited to ensure accuracy and consistency. (Biswas, 2024)

8. Stability Studies

To evaluate the long-term integrity of the formulation, stability studies are conducted by sealing the microspheres in screw-capped glass containers. The samples are then stored under the following diverse environmental conditions for a duration of 60 days:

- Ambient Humidity: To assess the impact of moisture on the polymer and drug.
- Room Temperature (27 ± 2°C): To simulate standard shelf-life conditions.
- Oven Temperature (40 ± 2°C): To perform accelerated stability testing.
- Refrigeration (5°C – 8°C): To determine the effects of cold storage.

At the conclusion of this period, the microspheres are analyzed to determine the remaining drug content and ensure the delivery system remains effective and chemically stable. (Verma, 2025)

Future Perspectives

The future of oral mucoadhesive microspheres lies in the transition from conventional polymeric carriers to sophisticated, stimuli-responsive "smart" delivery systems. While current research has established a strong foundation in mucoadhesion theories and basic polymer science, the next generation of therapeutics will likely leverage thiolated polymers and functionalized copolymers capable of forming covalent disulfide bonds with the mucus layer, significantly extending residence time. Furthermore, the integration of "Nano-in-Micro" hybrid systems offers a promising strategy to protect sensitive macromolecules, such as proteins and peptides, from enzymatic degradation while ensuring targeted delivery to specific intestinal regions.

Advancements in characterization will also benefit from the incorporation of Artificial Intelligence (AI) and molecular docking simulations, allowing researchers to predict polymer-mucin binding affinities *in silico* before moving to wet-lab synthesis. As the field progresses, a shift toward personalized medicine is anticipated, where microsphere properties are tailored to account for inter-patient variability in mucus thickness and turnover rates caused by age or disease states like Crohn's disease. Finally, for these systems to achieve clinical success, research must prioritize "Quality by Design" (QbD) frameworks to address the challenges of industrial scalability and regulatory approval, ensuring that these complex formulations can be manufactured with high reproducibility for global healthcare markets.

CONCLUSION

The development of mucoadhesive microspheres represents a transformative approach in pharmaceutical technology, successfully addressing the inherent limitations of conventional oral dosage forms. By extending the gastric residence time and ensuring intimate contact with the absorption site, these systems significantly enhance the bioavailability of drugs that otherwise suffer from poor absorption or rapid first-pass metabolism.

While various natural and synthetic polymers offer a wide range of mucoadhesive properties, the selection of the preparation method—whether solvent evaporation, spray drying, or ionotropic gelation—remains critical in determining the final particle size and drug loading efficiency.

Furthermore, the rigorous characterization and evaluation parameters discussed in this review provide a standardized framework for ensuring the safety and efficacy of these carriers. Despite the challenges associated with the rapid turnover of the mucus layer and the physiological variability of the gastrointestinal tract, mucoadhesive microspheres remain a highly promising platform. Future research directed toward multifunctional "smart" polymers and targeted delivery will likely bridge the gap between laboratory-scale innovations and commercial clinical success, ultimately providing more effective and patient-compliant therapeutic regimens.

REFERENCES

1. Ahmad, K. Z. (2024). Chitosan interaction with stomach mucin layer to enhances gastric retention and mucoadhesive properties. *Carbohydrate Polymers*, 333: 121926.
2. Ainurofiq, A. S. (2023). Chitosan as floating-mucoadhesive polymers in gastroretentive drug delivery. *Science, Engineering and Health Studies*, 23010002-23010002.
3. Alawdi, S. &. (2021). Mucoadhesive drug delivery systems: A review of recent developments.
4. *Journal of Scientific Research in Medical and Biological Sciences*, 2(1): 50-64.
5. Bader, R. A. (2013). Engineering polymer systems for improved drug delivery. *John Wiley & Sons.*
6. Baloğlu E, K. S. (2010). Design and formulation of mebeverine HCl semisolid formulations for intraorally administration. *AAPS PharmSciTech*, 11(1): 181–8.
7. Beg, S. R. (2021). Nasal mucoadhesive microspheres of lercanidipine with improved systemic bioavailability and antihypertensive activity. *Journal of Pharmaceutical Innovation*, 16(2): 237-246.
8. Bhalala, K. J. (2026). Microspheres: preparation methods, advances, applications, and challenges in drug delivery. *Biomedical Materials & Devices*, 4(1): 221-260.
9. Biswas, D. K. (2024). Biswas, D. K., Madhukar, V., Verma, A., Kachawa, V. S.Development and characterization of potential mucoadhesive microsphere for the treatment of cancer. *cademia. edu*.
10. Chauhan, V. A. (2022). A comprehensive review on mucoadhesive drug delivery. *Journal of Drug Delivery & Therapeutics*, 12(4-S): 199-209.
11. Chechare, D. D. (2024). Formulation and evaluation

of mucoadhesive microspheres of metronidazole. *Journal of Applied Pharmaceutical Research*, 12(1): 93-99.
12. Desai, V. A. (2025). Enhancing drug bioavailability through mucoadhesive technologies: A comprehensive review of delivery systems. *Biomedical Materials & Devices*, 1-19.
13. Deshmukh, R. H. (2023). Formulation and evaluation of oral mucoadhesive microspheres of ofloxacin for peptic ulcer use. *Trends in Sciences*, 20(9): 5751-5751.
14. Dewangan, H. K. (2021). Dewangan, H. K., Sharma Mucoadhesive microspheres of atorvastatin calcium: rational design, evaluation and enhancement of bioavailability. *Indian J. Pharm. Educ. Res.*, 19: 20.
15. Ganju, E. P. (2024). Mucoadhesive Microspheres: An Insight Review. *Int. J. Med. Phar. Sci.*, 14(3): 3.
16. Gopaiah, K. V. (2022). Formulation and characterization of mucoadhesive microspheres of aceclofenac. *Research Journal of Pharmacy and Technology*, 15(3): 981-988.
17. Gurung, B. D. (2020). An overview on microspheres. *Int. J. Health Clin. Res.*, 3(1): 11-24.
18. Hamdi, N. A. (2023). An insight into the use and advantages of Carbopol in topical mucoadhesive drug delivery system: A systematic review. . *Journal of Pharmacy*, 3(1): 53-65.
19. Jamkar, K. A. (2020). Formulation and evaluation of racecadotril mucoadhesive microspheres. *Int. J. Pharm. Pharm. Sci.*, 12(2): 55-61.
20. Kakkar, V. A. (2020). Role of microspheres in novel drug delivery systems: preparation methods and applications. *International Journal of Current Pharmaceutical Research.*, 12(3): 10-15.
21. Khan, S. G. (2020). Natural and synthetic polymers assisted development of lurasidone hydrochloride intranasal mucoadhesive microspheres. *Indian J Pharm. Edu. Res.*, 54(1): 213-222.
22. Kulkarni, R. F. (2023). Mucoadhesive drug delivery systems: a promising non-invasive approach to bioavailability enhancement. Part I: biophysical considerations. *Expert Opinion on Drug Delivery*, 20(3): 395-412.
23. Mady, F. M. (2021). Development and evaluation of alginate-gum blend mucoadhesive microspheres for controlled release of Metformin Hydrochloride. *Journal of Advanced Biomedical and Pharmaceutical Sciences*, 4(2): 111-118.
24. Mamatha, K. &. (2022). A review on: mucoadhesive drug delivery systems. *Journal of Innovations in Applied Pharmaceutical Science (JIAPS)*, 32-36.
25. Noreen, S. H. (2023). Formulation, statistical optimization, and in vivo pharmacodynamics of Cydonia oblonga mucilage/alginate mucoadhesive microspheres for the delivery of metformin HCl. *ACS omega,*, 8(6): 5925-5938.
26. Pandey, J. S. (2020). Development of nasal mucoadhesive microspheres of granisetron:A potential drug. *Drug research*, 70(08): 367.
27. Pathak, K. &. (2020). Introduction, theories and mechanisms of bioadhesion. *Bioadhesives in Drug Delivery*, 1-27.
28. Pattanayak, S. K. (2024). Preparation and Evaluation of Ketoprofen Loaded Mucoadhesive Microspheres. *Journal of Drug Delivery & Therapeutics*, 14(1).
29. Pawar, A. L. (2024). Chitosan fortified repaglinide gastro-retentive mucoadhesive microsphere with improved anti-diabetic attribute. *Intelligent Pharmacy*, 2(3): 441-449.
30. Raj, H. S. (2021). Mucoadhesive microspheres: A targeted drug delivery system. *Journal of Drug Delivery and Therapeutics*, 11(2-S): 150-155.
31. Safitri, F. I. (2021). Overview: Application of carbopol 940 in gel. In International Conference on Health and Medical Sciences (AHMS 2020). *Atlantis Press*, 80-84.
32. Sahu, Y. J. (2020). Mucoadhesive microspheres based formulation development of ziprasidone hydrochloride for nasal delivery. *Journal of Drug Delivery & Therapeutics*, 10(5).
33. Sangeeta, P. C. (2023). Formulation and evaluation of mucoadhesive microspheres of dolasetron for nasal delivery. . *Acta Biomed*, 94(1): 1091-1100.
34. Singh, I. D. (2021). Mucoadhesive pellets for drug delivery applications: a critical review. *Progress in Adhesion and Adhesives*, 155-169.
35. Singh, S. C. (2023). Mucoadhesive drug delivery system and there future prospective: are a promising approach for effective treatment? *Zhongguo Ying Yong Sheng Li Xue Za Zhi,*, 39: e20230005.
36. Stankovits, G. G. (2025). The adhesion mechanism of mucoadhesive tablets with dissimilar chain flexibility on viscoelastic hydrogels. *Materials Today Bio*, 30: 101416.
37. Subramanian, P. (2021). Mucoadhesive delivery system: a smart way to improve bioavailability of nutraceuticals. *Foods,*, 10(6): 1362.
38. Sun, X. S. (2022). Mucoadhesive phenylboronic acid conjugated chitosan oligosaccharide-vitamin E copolymer for topical ocular delivery of voriconazole: Synthesis, in vitro/vivo evaluation, and mechanism. . *Acta Biomaterialia*, 138: 193-207.
39. Verma, A. (2025). Formulation and Evaluation of Buccal Tablets with Drug-Loaded Microspheres.
40. *Abhi International Journal of Chemical and Pharmaceutical Science (AIJCPS),*, 1(1).