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Review Article

# Mucoadhesive Microspheres: An Insight Review

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## ABSTRACT

Mucoadhesive microspheres are an advanced drug delivery system designed to enhance the bioavailability and therapeutic efficacy of drugs by adhering to mucosal surfaces. These microspheres offer prolonged residence time, controlled drug release, and targeted delivery to specific mucosal sites, making them ideal for oral, nasal, ocular, and vaginal applications. This review aims to provide a comprehensive overview of the formulation strategies, characterization techniques, and therapeutic applications of mucoadhesive microspheres. A thorough literature search was conducted using databases such as PubMed, Scopus, and Web of Science. Articles focusing on the development, evaluation, and clinical applications of mucoadhesive microspheres were included. The review covers the selection of polymers, methods of preparation, and characterization techniques for assessing mucoadhesive properties, particle size, drug encapsulation efficiency, and in vitro/in vivo drug release profiles. The review identified various natural and synthetic polymers, including chitosan, alginate, and carbopol, as effective mucoadhesive agents. Preparation techniques such as emulsification, spray drying, and solvent evaporation were discussed, highlighting their impact on the physical and chemical properties of the microspheres. Characterization methods such as scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and mucoadhesion testing were examined. Studies demonstrated that mucoadhesive microspheres significantly enhance drug absorption and bioavailability by adhering to mucosal tissues and providing controlled drug release. Therapeutic applications span across multiple fields, including gastroenterology, pulmonology, and ophthalmology, with promising results in improving patient compliance and treatment outcomes. Mucoadhesive microspheres represent a promising drug delivery system with the potential to revolutionize the administration of pharmaceuticals. Their ability to adhere to mucosal surfaces, provide controlled and sustained drug release, and enhance bioavailability makes them suitable for various therapeutic applications. Future research should focus on optimizing formulation parameters, exploring novel mucoadhesive polymers, and conducting clinical trials to establish their efficacy and safety. The advancements in mucoadhesive microspheres hold significant promise for improving drug delivery and therapeutic outcomes across different medical fields.

**Keywords:** Mucoadhesive, Microspheres, Formulation, Characteristics, Mechanism, Applications

## INTRODUCTION

A lot of attention has been focused on developing new dosage forms that can regulate the release rate and target the active medication molecule to a specific spot.[1] One innovative medication delivery technology, microspheres are composed of a variety of polymers and have several potential uses.[2] Microspheres, often called microparticles, are microscopic spherical particles that usually range in size from 1 µm to 1000 µm.[3] Natural or synthetic polymers may be used to create the microspheres.[4] Incorporating mucoadhesive qualities into microspheres would further increase absorption and bioavailability of the medications, in addition to their potential for targeted and controlled/extended drug release.[5] By securing bacterial adhesions, plant lectins, antibodies, and other molecules, mucoadhesive microspheres improve medication targeting to the absorption site and increase close contact with the mucus layer.[6] Customised mucoadhesive microspheres stick to mucosal tissues in the mouth, nose, eyes, and urinary and gastrointestinal tracts, allowing for the localized and regulated release of medications.[7]

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## Advantages of Mucoadhesive Microspheres

Some of the advantages were found to be as follows:

1. Provide constant and longer therapeutic effect.
2. Reduces the frequency of daily administration and thereby improve the patient compliance.
3. Improve the absorption of drug hence improve the bio-availability of drug and reduce the chances of adverse effects.
4. The morphology of microspheres permits a controllable variability in degradation and drug release.
5. The shape of microspheres allows for a manageable range of disintegration and medication release.[8]

## Limitation of Mucoadhesive Microspheres

Some of the disadvantages were found to be as follows:

1. One possible change is the release profile of the formulations.
2. A number of variables, such as the diet and the pace of transit through the gut, mucin turnover rate, etc., might affect the release rate.
3. The rate of release might vary across different doses.
4. Toxic effects might result from the dose form's release pattern being compromised.
5. Crushing or chewing these dose forms is not an option.[9]

## Mucoadhesion

When two materials, at least one of which has a biological component, are held together by interfacial forces, this phenomenon is called bioadhesion. The way the polymers stick to the mucosal layer's surface is called "mucoadhesion".[10]

## Mucus Membranes

A number of bodily cavities, including those in the digestive and respiratory systems, are lined by mucus membranes, which are wet surfaces. Follicle cells release mucus. There are three different forms of mucus: a gel layer that sticks to the mucosal surface, suspended mucus, and luminal soluble mucus. Mucin glycoprotein, water, lipids, and inorganic salts are the main ingredients in any mucus gel. Mucus not only acts as a lubricant but also as a protective barrier.[11]

## Mechanism of Mucoadhesion

To recap, mucoadhesion refers to the process by which a medicine and an appropriate carrier cling to the mucosal layer. Wetting, adsorption, and interpenetration of polymer chains are the complex phenomena that make up mucoadhesion.[12]

## Mucoadhesion mechanisms

1. The wetting or swelling phenomena that occurs when a mucoadhesive delivery system comes into close contact with a mucosal membrane.
2. The mucoadhesive delivery system must penetrate either the tissue or the surface of the mucous membrane (interpenetration).[13]The method of mucoadhesion is shown in Figure 1.

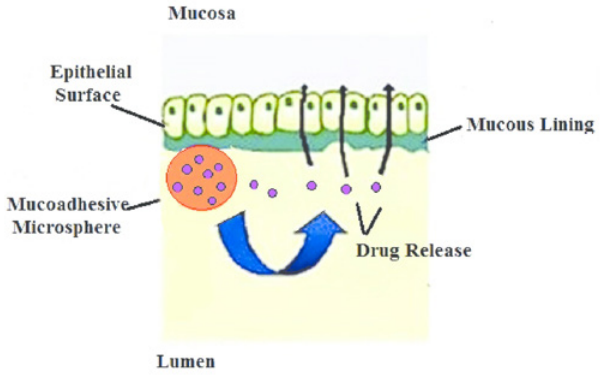


**Figure 1:** Intranasal Mucoadhesive Microspheres.

## Theories of Mucoadhesion

The following hypotheses are related in mucoadhesion:[14]

### 1. The Electronic Theory

In this idea, the mucoadhesive and mucosal membranes interact to create an electrical double layer during electron transfer.

### 2. The Wetting Theory

According to this principle, which is relevant to liquids, the stronger the affinity for adhesion, the smaller the contact angle between the liquid and the surface of the substrate.

### 3. The Adsorption Theory

In this view, intermolecular interactions such as hydrogen bonding, Vander Waal's forces, and others are responsible for the mucoadhesive adsorption onto the mucosal surface.

### 4. The Diffusion Theory

According to this idea, the polymer chains on the mucoadhesive surface diffuse into the mucosal surface, creating a network structure between the two.

### 5. The Mechanical Theory

It describes how mucoadhesion occurs, which is the consequence of liquid adhesives diffusing into the micro-cracks and imperfections of the mucoadhesive substrate, and how this forms an interlocking structure.

### 6. The Cohesive Theory

This hypothesis proposes that the major cause of mucoadhesion is the presence of like-molecule interactions between different molecules.

## Factors Affecting Mucoadhesion

These parameters determine how well a drug carrier system adheres to mucosal membranes. Factors Based on Polymers Molecular weight of the polymer, concentration of polymer, stereo chemical of polymer, chain length of polymer, hydration of polymer, physical considerations, swelling of the polymer, the applied force, the contact period, and the pH of the polymer-substrate interface. Mucin turnover rate and sick condition are physiological factors.[15]

## Materials used in the formulation of mucoadhesive microspheres

Mucoadhesive microspheres are made up by using mucoadhesivepolymers. Mucoadhesive polymers can be of either natural orsynthetic in origin. Mucoadhesive polymers that adhere to themucin-epithelial surface can be conveniently divided into threebroad classes:

- Polymers that become sticky on placing them in water andachieve their mucoadhesion due to stickiness.
- Polymers that adhere through nonspecific, noncovalentinteractions that is primarily electrostatic in nature.
- Polymers that bind to specific receptor site on tile self surface.[16]

## Classification of Mucoadhesive Polymers

There are various mucoadhesive polymers of synthetic and naturalorigin, which are classified in **Table 1**.

**Table 1: Mucoadhesive polymers of synthetic and natural origin**

| Synthetic Polymers | Natural Polymers |
|---|---|
| Hydroxyl ethyl cellulose (HEC) | Sodium alginate |
| Hydroxy propyl methyl cellulose (HPMC) | Tragacanth |
| Hydroxy propyl cellulose (HPC) | Gelatin |
| Poly hydroxyethyl methylacrylate | Pectin |
| Methyl cellulose (MC) | Karaya gum |
| Sodium carboxy methyl cellulose (Na CMC) | Locust bean gum |
| Poly(acrylic acid) polymers (carbomers, polycarbophil) | Xanthan gum |
| Poly vinyl pyrrolidone (PVP) | Chitosan |
| Poly ethylene oxide | Lecithin |
| Poly vinyl alcohol (PVA) | Guar gum |
| Ethyl cellulose (EC) | Soluble starch |

## METHODS OF PREPARATION OF MUCOADHESIVE MICROSPHERES

Mucoadhesive microspheres can be prepared by using differenttechniques like:

### 1. Complex Coacervation

This approach works on the principle that, given the right circumstances, a liquid precipitate may be separated by mixing solutions of two hydrophilic colloids. Coating material phase is made by dissolving immiscible polymer in an appropriate solvent; core material is mixed with coating polymer solution while stirring continuously in this process. Changing the temperature of the polymer solution, altering the pH of the medium, adding a salt, an incompatible polymer, a nonsolvent, or inducing a polymer-polymer interaction were all ways that microencapsulation was accomplished through phase separation. Coatings are often made into self-sustaining microspheres by using desolvation or thermal cross-linking processes to harden them.[17]

### 2. Hot Melt Microencapsulation

This approach was first used to manufacture microspheres of a polyanhydride copolymer containing sebacic acid and poly bis (p-carboxy-phenoxy) propane anhydride. Melting the polymer is the initial step in this method, followed by the continual mixing of the solid drug particles. To create a stabilised emulsion, the prepared mixture is first stirred into a non-miscible solvent, such as silicone oil, and then heated to a temperature higher than the polymer's melting point while swirling continuously. The resulting emulsion is filtered and washed with petroleum ether after cooling to harden the polymer particles. The microspheres are then removed.[18]

### 3. Single Emulsion Technique

The single emulsion approach is used to create the microspheres of natural polymers. Once the polymers and drug have been dissolved or dispersed in an aqueous media, they are transferred to an organic medium, such as oil, where they will form globules. The globules are then cross-linked using heat or chemical cross-linkers. Formula aldehyde, glutaraldehyde, diacid chloride, and other similar chemicals are used as cross-linkers.[19]

### 4. Double Emulsion Method

The most popular microencapsulation technique, first published in 1988 by Ogawa Y et al., is method number twenty. This process creates a primary water-in-oil emulsion by vigorously swirling an organic phase into a drug and polymer aqueous solution. Then, the emulsion was added to a large volume of water that already included an emulsifier, such as polyvinylpyrrolidone or polyvinyl alcohol, and stirred until the organic solvent evaporated, leaving behind solid microspheres. This process yielded several emulsions, weight/volume/weight. After that, the microspheres are rinsed and allowed to dry.[20]

### 5. Solvent Removal

Microencapsulation using this non-aqueous approach works well with polyanhydrides and other water-labile polymers. Step one of the process is to dissolve the drug in a volatile organic solvent. Then, while stirring, suspend the polymer-drug solution

in silicone oil that also contains methylene chloride and span 85. Step two involves adding petroleum ether and stirring again until the solvent is extracted into the oil solution, which is step. The next step was to dry the microspheres using a hoover.[21]

### 6. Ionotropic Gelation

Moss RD and Lim F created this technique. The gel-type polymers, like alginate, are dissolved in an aqueous solution using this method. Then, the active ingredient is suspended in the mixture and the mixture is extruded through a needle to create micro droplets. These droplets then fall into a hardening solution that contains calcium chloride while stirring at a low speed. The polymer is cross-linked and forms gelled microspheres by means of the divalent calcium ions that are present in the hardening solution.[22]

### 7. Phase Inversion Method

The procedure begins with the medication being added to a methylene chloride-based diluted polymeric solution. The resulting combination is then placed into an undisturbed bath of petroleum ether, a powerful non-solvent, in a ratio of 1:100. After that, the microspheres are cleaned with petroleum ether, let to air dry, and clarified.[23]

### 8. Spray Drying

The medication is dissolved or dispersed into the polymer solution and then spray dried using this technique. By adjusting the spraying rate, feeding rate of the polymer drug solution, nozzle size, and drying temperature, one may regulate the size of the microspheres using this approach.[24]

## DRUG LOADING IN MICROSPHERE

Microspheres may be drug-loaded in two main ways: either as they are being prepared, or afterwards, by incubating them with a drug solution. Different methods exist for loading active components, including physical entrapment, chemical coupling, and surface absorption. Although many other process factors, such as the presence of additives, preparation technique, heat of polymerization, agitation intensity, etc., may influence the maximal drug loading in microspheres, it was discovered that the drug may be integrated during production to accomplish this. After the microspheres are prepared, they may be loaded with medicine by incubating them with a high concentration of the drug in an appropriate solvent. Here, the microspheres may be drug-loaded in one of two ways: either by surface absorption or by the drug's penetration or diffusion through the microsphere's pores. The microspheres that contain the medication are then isolated by removing the solvent.[25]

## DRUG RELEASE KINETICS

When thinking about microspheres, drug release is crucial. The following are some of the many potential theoretical methods for drug release from the microsphere:

- The medication is released as a result of the polymer's erosion or breakdown.
- Drug self-diffusion via microsphere pores.
- Drug release from the polymer's surface.
- Electromagnetic or oscillating field-induced pulsed delivery.[26]

## EVALUATION OF MUCOADHESIVE MICROSPHERES

The microspheres are evaluated for the following parameters

### 1. Particle Size and Shape

Light microscopy (LM) and scanning electron microscopy (SEM) both can be used to determine the size, shape and outer structure ofmicrospheres.[27]

### 2. Surface characterization of the mucoadhesive microspheres

Scanning tunneling microscopy, scanning electron microscopy, and electron microscopy may all provide light on the surface morphology of microspheres and the morphological changes brought about by the breakdown of polymers. The surface morphological changes produced by the breakdown of polymers may be studied by incubating microspheres in phosphate buffer saline at different hourly intervals. A rougher surface of a microsphere promotes adhesion via higher mechanical interactions, while a smooth surface of a microsphere results in poor mucoadhesive properties.[28]

### 3. Surface Charge Study

Information about the mucoadhesive microspheres' surface charge, or zeta potential, may be extracted from photon correlation spectroscopy results. Using the in-built software that is based on the Helmholtz-Smoluchowski equation, one may compute the surface charge by connecting the observed electrophoretic mobility into zeta potential. Mucoadhesion processes, adhesive strength, and stability may all be predicted and controlled using zeta potential, an indication of particle surface charge. The structure, especially the charge, of the mucoadhesive polymers affects the mucus-polymer interactions that occur throughout the mucoadhesion process. Microsphere and mucus zeta potential measurements aid in the prediction of electrostatic interactions during mucoadhesion.[29]

### 4. Entrapment Efficiency

Keeping the microspheres in the buffer solution and letting them lyse is a good way to find out their entrapment efficiency or percent entrapment. Following filtration or centrifugation, the resulting lysate is tested for active components in accordance with the specifications of the monograph.[30]

The following calculation are used to compute the percent entrapment efficiency:

% Entrapment = Actual content/Theoretical content × 100

### 5. Swelling Index

One of the main requirements for the start of mucoadhesion is the swelling index, which shows how effectively the mucoadhesive microspheres can absorb fluids at the absorption site and swell at the absorbing surface.[31]The following equation may be used to get the value of the % swelling.

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

Where, $D_0$ = weight of dried microspheres; $D_T$ = weight of swelled microspheres

### 6. In-Vitro Release Study

For the purpose of studying the *in vitro* release profile in a dissolving medium that mimics the fluid present at the absorption site, standard IP/BP/USP dissolution equipment, such as a rotating basket or paddle type apparatus, are used, according to the monograph.[32]

### 7. Ex-Vivo Mucoadhesion Study

The microspheres' mucoadhesive property is tested on the intestinal mucosa of goats using phosphate buffer in accordance with the monograph. After rinsing the tissue samples, weigh the microspheres and immediately place the slides on a USP pill dissolving test machine with the appropriate support set at 37°C. We quantify the weight of the microspheres that leak out at various times.[33,34]

## CONCLUSION

Recent years have seen a surge of interest in innovative drug delivery technologies within the realm of contemporary pharmaceutical formulations. Since mucoadhesive microspheres keep the medication at the targeted location for longer, the absorption rate is higher, and the bioavailability is higher, they show promise as a method for controlled or sustained drug administration. It follows that mucoadhesive microspheres will also be crucial in the future of pharmaceutical research and development, especially in the use of cutting-edge methods and materials.

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**Conflict of Interest**

Declared none.

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**Authors' Contribution**

**Eisha Ganju:** Concept, Analysis, Checking

**Shubham Prajapati:** Literature Review, Writing manuscript

**Bhaskar Kumar Gupta:** Revision, Correction, Illustrations

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