

**REVIEW ARTICLE**

**Innovative Drug Delivery Systems: A Focus on Mucoadhesive Microspheres**

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**ABSTRACT**

*Mucoadhesive microspheres have become a viable drug delivery method, especially for resolving issues with oral administration. The focus of study is to provide a comprehensive review of the formulation and assessment of mucoadhesive microspheres. Medication is evenly distributed throughout spherical microparticles called microspheres, which are made of a polymer matrix. Due to their small particle size and efficient drug-carrying capability, mucoadhesive microspheres have become an essential part of innovative drug delivery systems. Numerous novel developments in the field of microspheres have been made, including mucoadhesive, hollow, and floating microballoons. It has been demonstrated that microspheres are a useful dosage form for controlled medication release. Drugs can be administered by microspheres in a number of ways, counting oral, parenteral, nasal, transdermal, ophthalmic, and intestinal. Mucoadhesive microspheres high residence time as they adhere to mucosal layer thereby giving prolonged and preside delivery of drug thereby increasing bioavailability of drug.*

**Keywords:** Mucoadhesive microspheres, polymer matrix, controlled drug delivery, mucosal surface, Prolonged release

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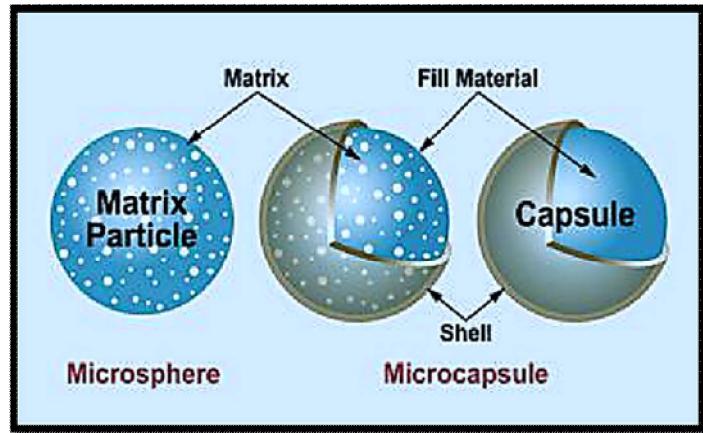
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**INTRODUCTION**

The oral route is mostly preferred as it is convenient, simple to use, and has higher patient compliance as compared to other routes. Low bioavailability in oral medication distribution, particularly for candidates whose absorption is restricted to the proximal gut; controlled release formulations must be developed to get around this restriction. [1,2] Many strategies have been devised to lengthen the drug's residence period. One such strategy is carrier technology, in which pharmaceuticals are combined with liposomes, noisome, nanoparticles, or microspheres as carrier particles to regulate medication release and absorption for a clever and focused approach. [1,3,4]. Microspheres are minute spherical particles ranging from 1 to 1000  $\mu\text{m}$  in diameter. Microspheres function as carriers in drug delivery. [5] In medication delivery systems, they are frequently employed as carriers, with the drug being enclosed in the microsphere and released under regulated conditions. Natural polymers are among the materials that can be used to create microspheres, which are intended to modify the properties of drug release and absorption for better therapeutic results. [5,6]



**Figure 1: Types of Microspheres**

Mucoadhesive microspheres, ranging in size from 1-1000 $\mu$ m, include microparticles and microcapsules. They are primarily composed of mucoadhesive polymer, featuring an additional outer layer.[3] Mucoadhesive microspheres have become evident strategy in drug delivery, particularly in overcoming challenges associated with oral route of administration. The purpose of the study is to have a detailed overview on formulation and evaluation of Mucoadhesive microspheres. Microspheres are spherical shaped microparticles in which drugs are uniformly dispersed in a polymer matrix. Mucoadhesive microspheres are a crucial component of innovative drug delivery as they have small particle size and effective drug carrying capacity. Various new advancement like mucoadhesive, radioactive, solid, hollow, floating microballoons have been done in case of microspheres. Microspheres have been proved an effective dosage form for controlled drug release. Microspheres can be used as a method for administering drugs through various routes like oral, Parenteral, nasal, transdermal, ophthalmic, colon etc. [5,7]

#### **IDEAL PROPERTIES OF MICROSPHERES**

- They should be compatible with drugs.
- They should release active ingredients in controlled manner
- They should be suitable for chemical modification.
- They must have large number of drug loading capacity.[8]

#### **ADVANTAGES:**

Microspheres present several advantages in various applications:

- 1. Controlled Drug Release:** A prolonged therapeutic effect is encouraged by the controlled and sustained medication release made possible by microspheres.
- 2. Reduced Dosing Frequency:** Because of the prolonged release feature, patients can often take their medications less often, which improves compliance.
- 3. Improved Bioavailability:** Improved drug utilization can result in increased bioavailability, which maximises the medication's therapeutic effect.
- 4. Targeted Delivery:** The drug's effectiveness can be increased by using microspheres that are made to be specifically delivered to certain tissues or organs.
- 5. Minimized Side Effects:** Microspheres have the potential to reduce the frequency or severity of side effects linked to fast medication release by managing the release profile.
- 6. Versatility:** They offer flexibility in pharmaceutical formulations by being able to be utilised with a variety of medications and in a variety of delivery methods.
- 7. Injectability:** Microspheres can be administered more easily because of their spherical form and small size, which make them suited for injection.
- 8. Stability:** Certain medications can benefit from the stability that microspheres provide, which keeps them from deteriorating and lengthens their shelf life.
- 9. Tailored Formulations:** Researchers can modify microspheres to contain particular medications, providing a platform for specialised drug delivery systems.
- 10. Potential for Combination Therapies:** Several medications can be combined into one microsphere to target different elements of an illness or to achieve synergistic effects.

Because of these benefits, microspheres are a useful tool in biomedical and pharmaceutical research for enhancing delivery of drugs. [9,10,11,12,13]

#### **DISADVANTAGE:**

**1. Cost:** The ingredients and complex methods required to generate microspheres might make the process costly.

**2. Release Uniformity:** It can be difficult to get a steady and regulated medication release from microspheres.

**3. Size Variability:** The performance of microspheres is affected by the difficulty of ensuring a consistent size distribution.

**4. Stability:** Stability problems with microspheres might arise, particularly in environments that change often.

**5. Encapsulation Efficiency:** The required material may or may not be effectively encapsulated within microspheres.

**6. Biocompatibility:** When using microspheres for drug delivery, potential adverse effects and body compatibility must be taken into account. [10,11,14]

#### **TYPES OF MICROSPHERES:**

##### **1. Mucoadhesive Microspheres:**

Mucoadhesive microspheres stick to mucosal membranes such as the nasal, ocular, buccal, and rectal surfaces by taking advantage of the ability of water-soluble polymers of adhering or sticking to mucosal membrane. In order to maximise therapeutic effects, this bio-adhesion encourages extended residence at the adhered site, guaranteeing intimate contact with the site of absorption. [15,16]

##### **2. Magnetic Microspheres:**

Drug distribution is greatly aided by magnetic microspheres, which localize medications to precise problem areas. By using magnetic targeting, they enable a decrease in the amount of medicine that is freely circulating; greater systemic doses can be exchanged with a lower quantity of magnetically focused drug. The magnetic receptivity of materials like chitosan and dextran to an applied magnetic field makes them popular choices for magnetic microspheres. [17,18]

##### **3. Therapeutic Magnetic Microspheres:**

Chemotherapeutic chemicals are delivered to liver tumours using therapeutic magnetic microspheres, providing tailored treatment. Moreover, medications that target proteins and peptides can be employed using this approach. Magnetic microspheres are used in diagnostics to generate nano-sized particles with supramagnetic iron oxides, which are useful for imaging liver metastases and distinguishing bowel loops from other abdominal structures. [19]

##### **4. Floating microspheres:**

Because floating microspheres are less dense than gastric or stomach fluid in volume, they can be buoyant in the stomach and decreases the pace at which the stomach empties. This design minimises variations in plasma concentration, lengthens the gastric residence time, promotes regulated drug release, and lessens the possibility of dose dumping. Crucially, it helps to prolong the therapeutic impact, which lowers the frequency of dose. [20]

##### **5. Radioactive microspheres:**

Radioactive microspheres with diameters between 10 and 30 nm are utilised in radioembolization therapy. They can become stuck in the first capillary bed they come across during administration since they are larger than capillaries. For some medical purposes, this tailored localization improves radioembolization therapy's accuracy and efficacy. [21,22]

##### **6. Polymeric microspheres:**

They can be classified as:

###### **a. Biodegradable Polymeric microspheres:**

Utilising natural polymers like starch, biodegradable polymeric microspheres provide benefits like biodegradability, biocompatibility, and bioadhesion. They have the property to form gel when comes in contact with aqueous medium, extending the duration of residence on mucous membranes and facilitating controlled, sustained release of drugs. [23]

###### **b. Synthetic Polymeric microspheres:**

Synthetic polymeric microspheres are mostly used as embolic particles, bulking agents, fillers, and drug delivery vehicles in therapeutic settings. [24]

## METHOD OF PREPARATION

### 1. Emulsion Solvent Evaporation

Mucoadhesive microspheres are frequently made by the emulsion solvent evaporation method. It involves dissolving a polymer in a solvent and emulsifying it in an aqueous phase with a mucoadhesive ingredient.

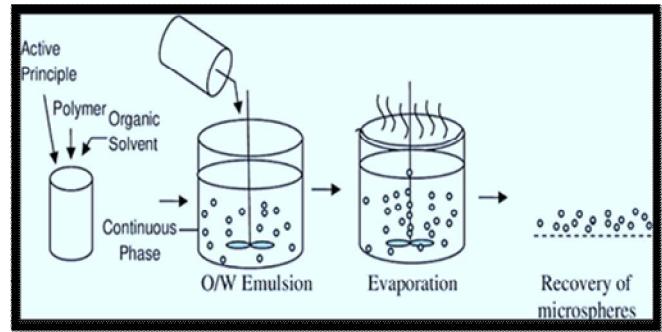


Figure 2: Emulsion Solvent Evaporation Method

Mucoadhesive microspheres are created by further solvent evaporation. For best outcomes, take into account variables including drying circumstances, emulsification technique, and polymer choice.[25]

### 2. Ionic gelation method:

The process of creating mucoadhesive microspheres using the ionic gelation method entails:

- a. Choosing a mucoadhesive polymer, like chitosan.
- b. Drug dissolution in a solvent and subsequent addition to the polymer solution.
- c. Inducing gelation by adding a cross-linking agent (such as tripolyphosphate) that has the opposite charge.
- d. Spherical microspheres forming during the gelation phase.

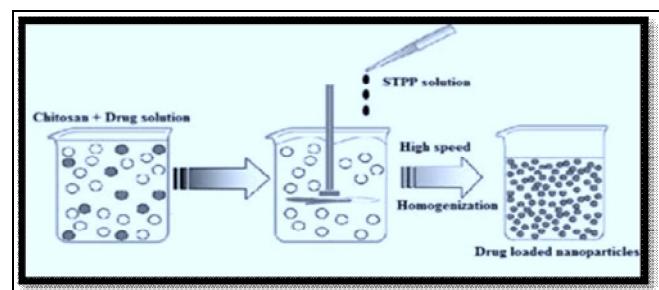


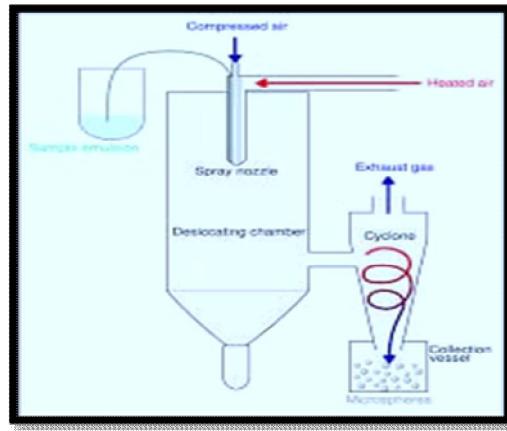
Figure 3: Ionic Gelation Method

- e. Cleaning and dehydrating the microspheres to get rid of extra chemicals.

This technique makes it easier to create mucoadhesive microspheres that release drugs under regulated conditions, improving absorption and extending the amount of time the drug remains at the target site.[26]

### 3. Spray Drying

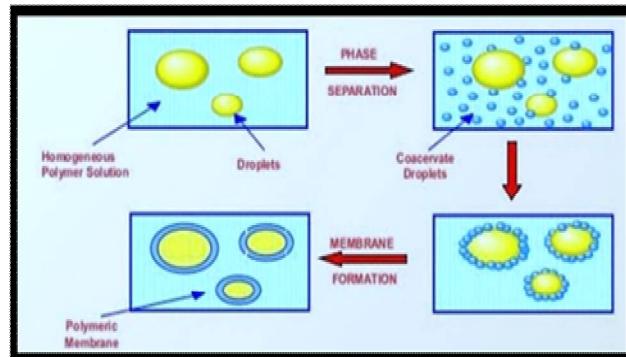
One common technique for creating mucoadhesive microspheres is spray drying. This method involves atomizing a solution of polymers and mucoadhesive compounds with a spray nozzle to create tiny droplets. After coming into contact with heated drying gas, these drops help to form solid microspheres. The polymer solution is usually combined with mucoadhesive agents, such as sodium alginate or chitosan, to improve adhesion to mucosal surfaces.



**Figure 4: Spray Drying Method**

The particular application and the intended release characteristics determine which polymers and mucoadhesive agents should be used. Spray drying offers several advantages for mucoadhesive microspheres, including excellent encapsulation effectiveness, control over particle size, and the ability to integrate both hydrophilic and hydrophobic medicines. It is crucial to optimize process parameters such as polymer concentration, inlet temperature and feed rate to achieve the desired properties of the microspheres.[27]

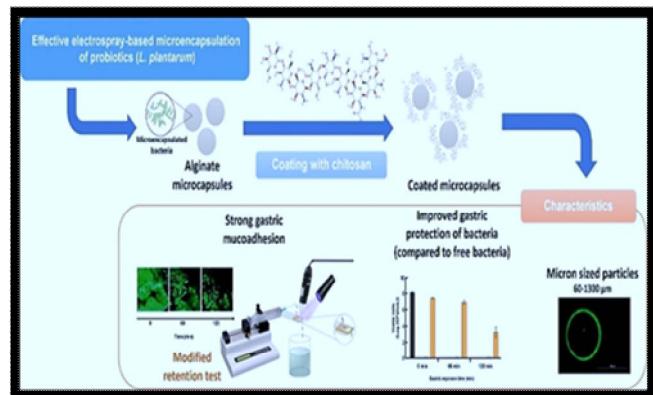
#### 4. Phase separation coacervation:



**Figure 5: Phase Separation Coacervation Method**

Using the phase separation coacervation approach, a medication is solubilized in a polymer solution to generate polymer-rich globules or micelles or droplets that are then formed into microspheres. After going through separation, these globules solidify in an aqueous or organic phase. Pure microspheres are subsequently obtained by washing and drying them. Improved drug encapsulation efficiency and controlled drug release are possible with this technique.[28]

#### 5. Electrospraying:

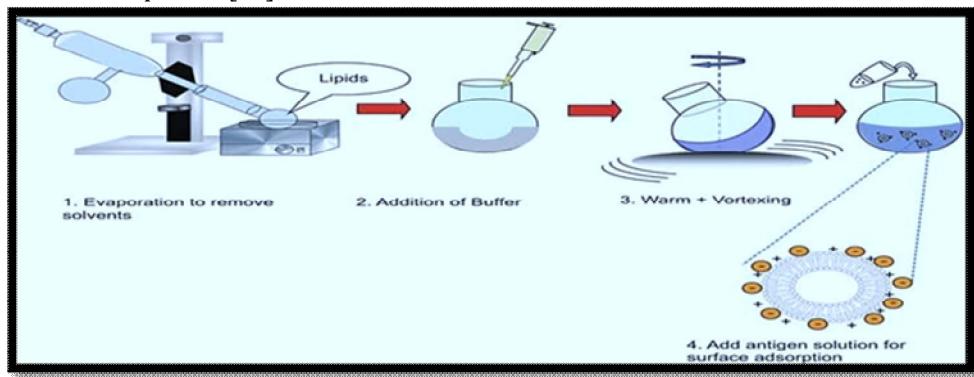


**Figure 6: Electrospraying Method**

A way for creating mucoadhesive microspheres is electrospraying. This process creates small droplets that solidify into microspheres by applying flow of current to a polymer solution. To improve adhesion to mucosal surfaces, the formulation can include mucoadhesive polymers like chitosan or alginate. The resultant mucoadhesive microspheres can be used to deliver drugs in mucosal tissues under regulated conditions, resulting in longer drug release and better therapeutic results.[29]

## 6. Rotatory Evaporation

Mucoadhesive microspheres are not directly prepared via rotary evaporation. Rather, emulsion solvent evaporation or coacervation are commonly used techniques to create mucoadhesive microspheres. In the last stages of microsphere preparation, rotary evaporation is frequently used to remove solvent and produce a dry powder. Techniques like emulsion or solvent evaporation with polymers like chitosan or alginate are good options for mucoadhesive microspheres. At mucosal surfaces, these polymers improve mucoadhesion and encourage sustained release. Following the creation of microspheres, remaining solvents can be eliminated by rotary evaporation to provide a dry powder that is suitable for additional uses. For exact instructions, always consult the relevant literature and guidelines for the manufacturing of mucoadhesive microspheres.[28]



**Figure 7: Rotatory Evaporation Method**

## THEORIES OF MUCOADHESION

There are certain theories for adhesion of microspheres to the mucus membrane. They are

1. The Electrostatic Theory
2. The Wetting Theory
3. The Adsorption Theory
4. The Diffusion Theory
5. The Mechanical Theory

### 1. The Electrostatic Theory

The attraction between charged molecules on mucosal surfaces and the sticky material is the basis for mucoadhesion, which is based on electrostatic interactions. According to this idea, the adherence of mucosal drug delivery systems is mostly dependent on electrostatic forces counting with hydrogen bonding and van der Waals interactions, which facilitate prolonged contact and improved drug absorption.[30]

### 2. The Wetting Theory

The capacity of a material to stick to mucosal surfaces is known as mucoadhesion. According to the wetting theory of mucoadhesion, an adhesive material's capacity to spread and improve contact and interaction on the mucosal surface is what determines whether adhesion is successful. When creating medical devices and medication delivery systems for mucosal administration, this can be highly important.[30]

### 3. The Adsorption Theory

As per adsorption hypothesis of mucoadhesion, adsorption forces mediate interactions between mucin molecules and a mucoadhesive material, which facilitate adherence to mucosal surfaces. This is important for bioadhesive formulations and medication delivery systems.[30]

### 4. The Diffusion Theory

According to the diffusion theory of mucoadhesion, molecular mobility and diffusion play a role in the interaction between mucoadhesive materials and mucous membranes. This idea contributes to the understanding of how materials stick to biological systems' mucosal surfaces.[30]

## 5. The Mechanical Theory

The term “mucoadhesion” describes a substance’s capacity to stick to mucosal surfaces. According to the mechanical theory, it is explained by the polymer chains in the mucin layer interpenetrating and entangled, forming a link. Knowing this aids in the development of medication administration methods that promote effective mucosal adhesion.[30]

## FACTORS INFLUENCING RELEASE OF DRUG

Many factors affect the release of medications from mucoadhesive microspheres.

### 1. Mucoadhesive Properties:

Mucoadhesive microspheres are primarily designed to stick to mucosal surfaces in order to extend the duration of medication contact with the intended target area. Surface charge, hydrogen bonding, and van der Waals forces in middle of the microspheres and mucosal tissue all affect mucoadhesion.

### 2. Polymer Selection:

Selecting the right mucoadhesive polymer is essential. Because of their mucoadhesive qualities, polymers like chitosan, sodium alginate, and carbopol are frequently utilised. The adhesiveness and general drug release properties of the polymer are determined by its molecular weight and structure.

### 3. Drug-Polymer Interaction:

Drug release may be impacted by how the medication and mucoadhesive polymer interact. For example, medication release rates and solubility may change as drug-polymer complexes arise.

### 4. Particle Size and Shape:

More surface area for mucoadhesion is sometimes provided by smaller particles, which may strengthen the adherence. The way that microspheres interact with mucosal surfaces can also be influenced by their form.

### 5. Drug Loading:

The kinetics of drug release are influenced by the quantity of drug enclosed in the microspheres. Longer-lasting sustained release may result from higher drug loading.

### 6. pH and Ionic Strength:

The pH and ionic strength can affect mucoadhesion and the subsequent release of the medication. pH variations could impact the rates of erosion and swelling of polymers.

### 7. Cross-linking Agents:

The amount of cross-linking in the polymer network is influenced by the cross-linking agents used during the manufacture of microspheres. Drug release and mucoadhesive strength are subsequently impacted by this.

### 8. Incorporation of Excipients:

Excipients can be added to change medication release patterns or boost mucosal penetration, such as release-modifying agents or penetration enhancers.

### 9. Biodegradability:

It is essential that mucoadhesive microspheres biodegrade. Biodegradable microspheres have the ability to progressively release the medication through regulated breakdown.

### 10. Temperature and Humidity

Mucoadhesive microspheres’ stability during administration and storage may be impacted by environmental factors, which could have an effect on how well they work.

The achievement of the intended drug release profile and therapeutic efficacy in the design of mucoadhesive microspheres depends on comprehending and optimising these aspects. Please don’t hesitate to inquire if you need more information on any subject or if you have specific questions. [31]

## EVALUATION PARAMETERS

Parameters of evaluation for mucoadhesive microspheres:

### 1.) Mucoadhesive Strength:

It is amount of force required to separate the microspheres from the mucosal surfaces using a tensiometer, for example. Longer residence at the target location is ensured by stronger mucoadhesive agents, which improves drug absorption and therapeutic efficacy.

### 2.) Particle Size and Distribution:

Utilise methods such as scanning electron microscopy or dynamic light scattering to ascertain the microspheres’ homogeneity and size distribution. Proper contact with mucosal surfaces and consistent drug administration are made possible by uniform particle size.

### **3.) Surface Morphology:**

Examine the microsphere surface using microscopy research to check for any abnormalities, homogeneity, and smoothness. An even and smooth surface reduces the possibility of discomfort and encourages efficient mucoadhesion.

### **4.) Drug Loading and Release:**

To measure the amount of medication encapsulated and investigate release kinetics under physiologically realistic settings, use analytical methods. Guarantees the best possible drug delivery through regulated release schedules, preventing sudden releases and attaining long-term therapeutic concentrations.

### **5.) Swelling Behavior:**

When microspheres come into touch with mucosal fluids, keep an eye on their swelling using methods such as gravimetric analysis. Knowing how microspheres swell aids in forecasting how they will interact with mucosal surfaces and take in liquids.

### **6.) In vitro Release Studies:**

Measure drug release over time in release tests conducted under physiologically realistic settings. Offers information on the kinetics of release, assisting in the formulation optimisation for targeted medication release patterns.

### **7.) Rheological Properties:**

Rheological methods can be used to evaluate viscosity and flow characteristics. Developing formulations that are easy to administer and retain requires an understanding of rheological behaviour.

### **8.) Surface Charge:**

To assess the electrostatic interactions between mucosal surfaces and microspheres, measure the zeta potential. Mucoadhesion is influenced by surface charge, and it is essential to comprehend these interactions in order to optimise formulation.

### **9.) Cytotoxicity and Biocompatibility:**

To evaluate the effect of microspheres on cell health, carry out investigations on cell viability. Significance: Guarantees mucoadhesive microspheres' safety for biological applications.

### **10.) In vivo Studies:**

Assess mucoadhesive performance, biodistribution, and therapeutic efficacy using animal models. Offers insight into the behaviour of microspheres inside a living system, directing future research and possible therapeutic uses.

### **11.) Stability Studies:**

Put mucoadhesive microspheres through different storage scenarios and track how the important metrics change over time. Assures the formulation's stability and shelf life, which are essential for real-world uses.

Researchers can fully comprehend and optimise mucoadhesive microsphere compositions for particular therapeutic purposes by carefully evaluating these parameters. [32,33,34,35,36]

## **APPLICATIONS OF MUCOADHESIVE MICROSPHERES**

Applications for mucoadhesive microspheres in biomedicine and pharmacology are numerous.

### **1.) Gastrointestinal Drug Delivery:**

Medication delivery to the gastrointestinal tract that is specifically targeted for diseases like inflammatory bowel disease. Enhanced medicine absorption and extended release at particular digestive system locations.

### **2.) Oral Vaccination:**

Controlled antigen release to boost the immune system in preparation for oral vaccinations. Vaccinations delivered effectively and without the need for shots.

### **3.) Ophthalmic Drug Delivery:**

Drugs with prolonged release on the surface of the eye to treat eye conditions. Enhanced bioavailability and extended duration of therapeutic benefit.

### **4.) Vaginal Drug Delivery:**

Targeted medication administration for ailments like contraception or vaginal infections. Increased medication retention in the mucosa of the vagina.

### **5.) Nasal drug delivery**

Medication administered specifically to the nasal mucosa to treat infections or allergies. Decreased adverse effects and increased patient compliance.

## **6.) Intravesical Drug Delivery:**

Medication administration in the bladder under controlled circumstances to treat disorders relating to the bladder. Reduction of adverse systemic effects.

## **7.) Periodontal Disease Treatment:**

Antibacterial medicines delivered locally to treat periodontal infections. Improved treatment effectiveness with a lower systemic exposure

## **8.) Therapy:**

Anticancer medications delivered specifically to mucosal membranes. Reduction of systemic toxicity and enhancement of therapeutic results.

## **9.) Cosmetic and Dermatological Applications:**

Controlled release of active chemicals for long-lasting skin benefits in cosmetic compositions. Improved dermatological medication administration for skin ailments.

## **10.) Anti-Infective Agents:**

Antibacterial compounds released under control to treat infections in mucosal tissues. Prevention of antibiotic resistance by long-term medication exposure.

These uses demonstrate how adaptable mucoadhesive microspheres are for precisely administering therapeutic substances, minimising side effects, and enhancing patient outcomes in a range of medical situations. [28]

## **CONCLUSION**

Based on the aforementioned study, we may draw the conclusion that mucoadhesive microspheres offer a flexible and exciting new approach to drug delivery that can help with oral administration's drawbacks. Significant benefits like increased bioavailability, fewer dosage intervals, targeted distribution, and less side effects are provided by their capacity to stick to mucosal surfaces in conjunction with controlled drug release. In applications related to medicine and biology, mucoadhesive microspheres show exceptional adaptability. Their ability to stick to mucosal surfaces allows for precise and targeted medication delivery, which reduces systemic side effects and eventually improves therapeutic efficacy. Mucoadhesive microspheres play a fundamental role in enhancing patient outcomes in a variety of medical contexts, including gastrointestinal medication administration, oral immunisation, ocular drug delivery, and more.

## **CONFLICT OF INTEREST**

The author declares that there is no conflict of interest.

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