MUCOADHESIVE MICROSPHERES: A REVIEW ON EMERGING TREND IN NASAL DRUG DELIVERY

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ABSTRACT
Over the past few decades, there has been a considerable shift from conventional drug delivery system to novel drug delivery system in pharmaceutical field. The main reason behind this approach is to increase the safety, efficacy and reduce the toxicity of drugs. Microspheres are one such novel drug delivery system that increases plasma drug concentration of drug, prolongs its action, which in turn reduces dosing frequency of dosage forms. Patient compliance also increases when sustain release action is attained. The advantage of mucoadhesive microspheres is that, it remains in close contact with the mucous membrane due to bio-adhesion thus releasing the drug at targeted site and increasing bioavailability. The aim of this article is to understand mucoadhesion and to emphasize its application in nasal drug delivery system.

KEYWORDS: Microspheres, Mucoadhesion, Patient compliance, Bioavailability, Nasal Drug Delivery.

INTRODUCTION
The aim of pharmacist is to develop a formulation that has maximum bioavailability with minimum side effects. The objective of this article is to review a dosage form that promises to increase patient compliance by reducing the frequency of dosing and with increased bioavailability. In order to contribute to the novel drug delivery system formulations, an approach towards reviewing microspheres is being done in this article.

The concept of packing microscopic quantity of material within microspheres dates to 1930s.
the work of Bungenberg Ded Jong and Co. on the entrapment of substances coacervates. Microspheres are solid spherical particles ranging in size from 1-1000 micron. They are free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature. Microspheres are employed to deliver the drug as it has the ability to produce targeted response and control release action. Mucoadhesion is a process in which there is bio-adhesion of two surfaces of which, one is biological membrane and another is polymer. When microspheres are formulated as mucoadhesive microspheres, the efficacy of the formulation increases drastically. Mucoadhesion tends to enhance the contact time of drug with mucous membrane, hence extended release action is achieved. Since mucoadhesive microspheres provide a local action, dose of the drug decreases as the plasma drug concentration increases hence, toxicity of drug can be lowered. These formulation ideas can be applied to any mucosal tissues- present in eye, nasal cavity, urinogenital tract, GI tract etc. However, this review article especially focuses on problems of nasal cavity and application of mucoadhesive microspheres on it\[11]\.

**Classification of microspheres**

![Classification of microspheres](image)

**Fig. 1: (Classification of microspheres).**

**Characteristics of An Ideal Microspheres**\[1,3,6,10]\:

- Microspheres should have the ability to incorporate high concentration of the drug.
- The preparation of microspheres should be stable with clinically accepted shelf life.
- It should have controlled particle size.
- They should be compatible with all the excipients.
Microspheres should release active ingredient with a good control over a wide time scale.

**Advantages of Microspheres** \(^{[1,3,6]}\)

- Particle size can be reduced for enhancing solubility of poorly soluble drugs, in microspheres.
- Provide constant and prolonged therapeutic effect.
- Provide constant drug concentration in blood thereby increasing patient compliance.
- Decrease dose and toxicity.
- Reduce the dosing frequency and thereby improve patient compliance.
- Convert liquid to solid to mask the bitter taste.
- Better drug utilization improves the bioavailability and reduce the incidence or intensity of adverse effect.
- Protect the drug from enzymatic and photolytic cleavage hence, found to be the best for drug delivery of proteins.

**Disadvantages of Microspheres**

- The cost of formulating control release formulations are slightly higher as compared to conventional drug dosage form.
- Reproducibility of this formulation is less.
- Conditions like temperature, PH, solvent addition etc effect the stability of encapsulated particle.
- The environmental impact of the degradation product of the polymer matrix produced in response to heat, hydrolysis, oxidation or biological agents.

**Types of Microspheres** \(^{[1,12,16]}\)
Bio Adhesive/Mucoadhesive Microsphere
Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymer. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as Mucoadhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption side and produces better therapeutic action.

Magnetic Microspheres
These kind of microspheres are used, when the drug is to be delivered on targeted site. In this type of microspheres, very small quantity of drug that are magnetically charged is required to produce response. Here, magnetic careers produces magnetic field when they receive response from magnetic materials that are incorporated in various polymers. They are used for two purposes.
1. Therapeutic purpose; example for treatment of tumours
2. Diagnostic purpose; example for imaging liver metastases.

Floating Microspheres
These microspheres is based on the principle of density difference. As the name suggest, floating microspheres will float in gastric fluid as the density of floating microspheres is less as compared to gastric fluid density. The main advantage is prolonged therapeutic effect, reduced dosing frequency.

Radioactive microspheres
They are the microspheres that ranges from size 10-30nm. They are larger than the diameter of capillaries and hence get trapped when they try to cross them. Radioactive microspheres are injected directly into arteries so they deliver high dose as compared to other forms of microspheres.

Polymeric microspheres
They are of two types

- **Biodegradable Polymeric Microspheres:** They are widely used because it prolongs the residence time with mucous membrane due to its swelling property with aqueous medium. However its main disadvantage is that it has a complex drug loading mechanism and uncontrolled drug release pattern.
- **Synthetic Polymeric Microspheres:** They are becoming more popular as it is safer and biocompatible with other adjuvants. However, they tend to migrate from the site of injection and may cause embolism and organ failure.

**Mucoadhesive Microspheres, An Emerging Tool In Nasal Drug Delivery**[^5,15]

The term “MUCOADHESION” was coined for the adhesion of the polymers with the surface of the mucosal layer. It utilises property of sticking of two surfaces to each other, one of which is biological membrane and the other is polymer, and it is possible due to the interfacial forces that exist between these two membranes. Various polymers are used to bind to mucous membrane and they are of either synthetic or natural origin. The property of mucoadhesion can be used in the areas like buccal cavity, urogenital tract, rectum, vaginal area, nasal cavity.

**Types Of Polymers Used In Mucoadhesive Microspheres**[^13,14,17]

![Fig. 2: (Types of Polymers).](image)

Principle of Mucoadhesion

The principle of mucoadhesion involves formation of mucoadhesive bond between polymer and mucous membrane by 3 steps:

1. **Contact stage**: wetting and swelling of the polymer.
2. **Interpenetration stage**: interpenetration occur between polymer chains of microspheres and mucous membrane.
3. **Consolidation stage**: formation of bond between the entangled chains.

![Fig. 3: (Stages of Mucoadhesion).](image)

Theories of Mucoadhesion

![Fig. 4: (Theories of Mucoadhesion).](image)
Wetting Theory
This theory states that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive among the substrate surface.

Diffusion Theory
According to this theory, the polymer chains and the mucous mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucous depends on the diffusion coefficient and the time of contact. The diffusion coefficient in terms depends on the value of molecular weight between crosslinking and decreases significantly as the cross linking density increases.

Fracture Theory
This theory is based on the principle of the force required to break the polymeric chains of mucin layer is the total strength of the adhesive bonds between polymer and biological membrane. This force can be calculated using this formula:
\[ G = \left( \frac{E(e/l)}{l} \right)^{1/2} \]
where:
- \( G \) = Fracture strength
- \( E \) = Young's modulus
- \( e \) = Fracture energy
- \( l \) = critical crack length

Mechanical Theory
This theory states the formation of mechanical bond between two surfaces. The formation of the bond is similar to the interlocking systems.

Electronic Theory
According to this theory there is difference in electronic structure of mucous membrane and polymer system, which results in formation of electronic gradient between them. As a result, exchange of electron occur between these two systems leading to formation of electronic bilayer. This interfacial electronic bilayer helps in mucoadhesion.

Adsorption Theory
This theory involves the formation of two bonds, one is the formation of primary bond between mucin and bio-adhesive systems which is covalent in nature. The secondary bond is the weak bond resulting due to Van Der Waal’s forces, hydrogen bonding and hydrophobic
interaction. Mucoadhesion occurs due to surface energy present in mucin and mucoadhesive systems.

**Overview of nose and nasal cavity**
In order to understand the advantages of mucoadhesive systems in nasal drug delivery, it is important to understand basic nasal anatomy and physiology. The nose is the primary organ of smell of the body and also functions as an important part of respiratory system. Inside the nose there is a nasal cavity and hollow space known as sinus that are lined by mucous membrane. People have four pairs of sinuses, hollow spaces behind the bones of faces. The paranasal sinuses have the same mucous membrane lining the nose. They produce a slimy secretion called as mucous. This keeps the nasal passage moist and trap dust and germs.

The human nasal extends from the external opening, the nostrils, to the pharynx where it connects to the lower respiratory system. The nasal cavity is divided into 3 sections, vestibule, respiratory and olfactory region 2.

![Nasal Cavity Diagram](image)

**Fig. 5:** (Anatomy of nasal cavity).
List of Various Diseases Affecting Nose and Nasal Cavity

- Nasal polyp.
- Nasal septal abscess.
- Nasal septal hematoma.
- Nasal septum deviation.
- Nasal septum perforation.
- Nasal vestibulitis.
- Nonallergic rhinitis.
- Nosebleed.

In order to treat various nasal problems, an effective dosage form is required that promises to provide utmost safety, efficacy and least toxicity. The conventional and traditional dosage forms used to treat nasal cavity infections have many drawbacks, so to overcome these drawbacks, there is a need to find alternative that can serve better.

**DOSAGE FORMS OF NASAL DRUG DELIVERY**

![Diagram of various dosage forms of nasal drug delivery]

Fig. 6: (various dosage forms of nasal drug delivery).

Advantages of Microsphere Over Other Dosage Forms In Nasal Drug Delivery

Microsphere technology has been widely applied in designing formulations for nasal drug delivery and is more superior to other dosage forms. Microspheres also protect the drug from enzymatic degradation and thus give sustained drug release, prolonging its effect. Due to their
ability of sustain release, they tend to decrease the dosing interval frequency, hence eventually increases patient compliance. The dose of any potent drug is also decreased in microspheres formulation as they are target specific and toxicity of any drug can therefore be reduced.

**Challenges That Mucoadhesive Microspheres Overcome In Treating Nasal Disorders**

- Pathological conditions like cold, allergies
- Rapid removal of therapeutic agents from the site of action
- Rapid mucocilliary clearance
- Quick enzymatic degradation of administered drug
- Poor physiochemical properties of drug
- Low permeability of nasal mucosal membrane

Due to the ability of mucoadhesive microspheres, to overcome these problems, they are preferred over traditional dosage forms, and are new in trend in treating nasal disorders.

**Methods of Preparation of Microspheres**

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<td>SPRAY DRYING AND SPRAY CONGEALING</td>
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**Fig. 7**: (Methods of preparation of microspheres).

**Spray Drying**: In this technique, the polymer is dissolved in a suitable volatile organic solvent. The drug which is the solid form is slowly and carefully added in the polymer solution with high speed homogenization. The dispersion that is formed is atomized in hot
stream of air. Due to atomization there is formation of fine droplets. These fine droplets contain solvent, which evaporates leading to formation of microspheres. The microspheres that are formed are then vacuum dried to remove any solvent present in them. The major advantage of this method is that it can be done on lab scale under aseptic condition.

**Fig. 8: (Spray drying technique).**

**Solvent Evaporation:** This process is carried out in a liquid manufacturing vehicle. Here two immiscible liquid phases are taken. The polymer solution is then dispersed in a volatile solvent, both being immiscible with each other. The drug to be microencapsulated is dissolved in polymer solution. With careful mixing of these two solutions there is formation of microcapsule, due to dispersion in immiscible solvent. Later heat is applied to this microcapsule to remove the solvent present in it.

**Single emulsion technique**

**Fig. 9: (Single emulsion technique).**
In this technique, firstly the polymer is dissolved in aqueous medium followed by its dispersion in non-aqueous medium. Then heat is applied to achieve cross linking of polymers. Various cross linking agents are also employed to achieve cross linking eg. Glutaraldehyde, formaldehyde and acid chloride as heat treatment cannot be applied for thermolabile substances. After preparation they are subjected to centrifugation, washing and microspheres are formed.

**Double Emulsion Technique**

This method is applicable for natural and synthetic polymers. In this method there is formation of multiple emulsions or the double emulsion of type w/o/w and is suitable for water soluble drugs, peptides, proteins and the vaccines. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. Active ingredients is present in protein dispersed phase. The continuous phase encapsulates the protein part. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol. This results in the formation of a double emulsion. This emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction method.

**Phase Separation and Coacervation Technique**

It is the most simple method to prepare microspheres. In this process, the polymer is dissolved in solvent to form a solution. This process is used for water soluble agents like peptides, proteins etc. The principle of coacervation is to decrease the solubility of polymer in organic phase so that there is formation of coacervates. In this method, formation of dispersion of drug particles in a solution of the polymer and a polymer that is incompatible with the polymer solution is added. Hence there is formation of small globule like particle. It can also be used for the preparation of matrix types for hydrophobic drug e.g. steroids.

**Spray Drying and Spray Congealing**

This technique is based on the process of drying of polymer and drug in air. The first process involves dissolving drug in organic solvent and subject it to high speed homogenization, which leads to formation of small mist. It is then evaporated to remove excess of solvent. The main advantage of this process is that it can be made on lab scale under aseptic conditions. Thiamine mononitrate and sulpha Ethylthiadizole are microencapsulated by using spray congealing method. However due to sudden drying and congealing there are chances of microspheres being porous in nature.
Solvent Extraction

This method is employed when there is need to remove solvent from the formed aqueous or non-aqueous phase. In this method oil phase can be extracted with aqueous phase like water. The advantage of this process is that it decreases hardening time of microspheres. Rate of solvent removal extraction is dependent on temperature of water used for extraction, ratio of emulsion volume to water and solubility of polymer in solvents.

Fig. 10: (SOLVENT EXTRACTION PROCESS).

Special Methods To Prepare Mucoadhesive Microspheres\textsuperscript{[5]}

Table no. 1:

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<tr>
<th>1. Air suspension process</th>
<th>2. Hot melt microencapsulation</th>
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<td>7. Wet inversion technique</td>
<td>8. Complex coacervation technique</td>
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Evaluation Parameters of Microspheres\textsuperscript{[2,4,5,7]}

1. Particle shape and size: The size and shape of formed microspheres are evaluated with the help of conventional light microscopy (LM) and scanning electron microscopy (SEM).

2. Degradation behaviour pattern: The amount of microspheres degraded or the surface chemistry of microspheres can be determined using electron spectroscopy for chemical analysis (ESCA).

3. Angle of repose: The flow property of formed microspheres are evaluated by allowing the powder mass to flow through a funnel that is vertically kept on a horizontal surface. Powder is allowed to flow through funnel and a heap of powder mass is formed on horizontal surface. Angle of repose can be calculated using formula,
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\[ \tan \Theta = \frac{h}{r}, \]

where, \( h \) = height of the cone
\( r \) = radius of the cone

4. **Bulk density**: This can be calculated using formula,
   
   \[ \text{Bulk density} = \frac{\text{mass of microspheres}}{\text{bulk volume}}. \]

5. **Tapped density**: It can be calculated using formula,
   
   \[ \text{Tapped density} = \frac{\text{mass of microspheres}}{\text{tapped volume}}. \]

6. **Drug entrapment efficiency**: It can be defined as the actual amount of drug that a microsphere hold. It can be calculated using formula,
   
   \[ \text{Entrapment} = \frac{\text{Actual content}}{\text{theoretical content}} \times 100 \]

7. **Swelling index**: This can be calculated using a phosphate buffer solution Ph 6.8. The microspheres are dissolved in this solution and its mass is calculated after letting the microsphere swell in it. The swelling index can be obtained using formula,
   
   \[ \text{Swelling index} = (\text{mass of swollen microspheres} - \text{mass of dried microspheres}) \times 100 \]

8. **In vitro tests**: This can be studied by dissolving microspheres in phosphate buffer pH 7.4 in rotating paddle type apparatus. During agitation, the samples are taken out and they are analysed, the amount of sample taken out is replaced with fresh solvent.

9. **Mucoadhesive test**: This test is done to study the mucoadhesive property of microspheres. In this test freshly cut piece of pig intestine is used (5cm long), cleaning and washing is done with isotonic solutions. Weighed amount of mucoadhesive microspheres are attached to the mucosal surface and this is placed in phosphate buffer pH 6.8 at 37˚. The duration of complete washing of microspheres from pig intestine is to be recorded.

![Fig.11: (Mucoadhesive test on pig ileum).](image-url)
10. **Stability studies:** The stability of microspheres can be checked by exposing them under different conditions of temperature, pressure, moisture, humidity for several months and later they can be evaluated for their stability.

**Applications of Microsphere**[^7,16]

1. Mucoadhesive microspheres are used to formulate, controlled and sustained release dosage forms.
2. Mucoadhesive microspheres have a wide usage in the buccal, vaginal, GI, ocular, nasal, transdermal and colonic drug delivery system.
3. They are used in areas like where dose of drug is to be decreased, as it is target specific.
4. Mucoadhesive microspheres are used in increasing patient compliance, since they provide long residence time, hence frequent administration of drug is not necessary.
5. Any drug having obnoxious odour, taste can be masked by formulating them into microspheres.
6. Microspheres have also found potential applications in injection, inhalation, sprays etc.
7. They are used extensively in the field of diagnostics e.g. temperature sensitive microspheres are used to detect presence of tumours.
8. They are also used in field of biotechnology, e.g. Microencapsulated cells are used for the production of recombinant technology.

**CONCLUSION**

From the detailed investigation and reviewing literatures, it has been concluded that, microspheres promise to serve as a better dosage form as compared to traditional way of drug delivery. It has also been observed that mucoadhesive microspheres possess more potency, as they are target specific. Moreover, they are widely preferred in nasal drug delivery, because they increase bioavailability, residence time and thereby improve patient compliance. They are also easy to formulate and administer to the patients suffering from nasal disorders. Since microspheres contribute a lot in all the spheres of pharmaceutical drug delivery, they will definitely have a vital role in the field of medicine in upcoming days.

**REFERENCES**


16. C.Nithya shanthi, Dr. Rakesh Gupta, Arun Kumar Mahato, Traditional and emerging