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Mucoadhesive Microspheres: A Novel Approach

[1]Reshma B. Suryawanshi, [2]Sujata D. Katkar, [3]Gangasagar B. Jalane, [4]Ganesh A. Jawalekar, [5]Abdul Azeem A. Syed,

[1]Student, [2]Student, [3]Student, [4]Student, [5]Assistant Professor

[1]Shivlingeshwar College of Pharmacy, Almala, Maharashtra.

Abstract: Mucoadhesive Microsphere Drug Delivery System (MMDDS) is an innovative approach to novel drug delivery designed to boost therapeutic efficacy while minimizing side effects.Mucoadhesive microspheres are small, spherical carrier particles (1-1000 µm in diameter) with a drug core encapsulated by a polymer-coated shell. These microspheres adhere to mucosal surfaces, and improve the residence time of the dosage form at the absorption site, cause effective absorption and enhanced bioavailability due to high surface volume to intimate contact with the mucus membrane. This system is also able to enable controlled drug release and improve therapeutic performance and high safety profile.Mucoadhesive microspheres are emerging as a perfect targeting mechanism for both local and systemic effects across various routes of administration, including oral, buccal, nasal, ocular, ophthalmic, rectal and vaginal regions.This review provides the comprehensive overview of mucoadhesive microspheres, including theories of mucoadhesion, types of mucoadhesive polymers, methods of preparation of microspheres, their evaluation, advantages, disadvantages and potential applications.

Index Terms - Microsphere, Mucoadhesive microspheres, Mucoadhesion, residence time, Novel Drug Delivery System

1. Introduction

The growing need for enhanced therapeutic efficacy and reduced side effects in pharmacy domain has sparked a new innovation, focusing on novel drug delivery system. The development of controlled release drug delivery system of a drug helps to improve its therapeutic benefits & minimizing side effects or problems of conventional therapy. The action of drug can be improved by developing Innovative drug delivery system, such as mucoadhesive microsphere drug delivery system. Mucoadhesive microspheres are contacted closely with mucous membrane & release drug at the site of action, which increases bioavailability & show systemic and local effects. In the formulation of conventional drug products, no deliberate effort is made to modify the drug release rate, have certain restrictions. Microspheres have small size & effective carrier capacity, hence they play significant role in drug delivery system.

1.1 Microsphere

Microspheres are common constituent of microparticulate drug delivery system. Microspheres are small spherical particles of diameter 1-1000 µm. Various natural and synthetic materials are used to prepare microspheres such as polymers, glass, ceramic etc. Microspheres can be characterized as matrix systems in which the drug is homogenously dispersed, either dissolved or homogenously suspended, also called microparticles. The dosage forms manufactured using microspheres improved the release rate and targeted activity of medications, with increasing bioavailability & absorption.

1.2 Mucoadhesive Microspheres

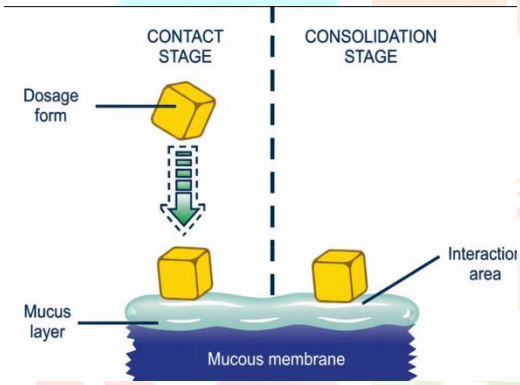
Recent advancements in both polymer science and drug carrier technologies created the innovative drug carrier such as mucoadhesive microspheres, which applies the bioadhesion in drug delivery system. Microparticles and microcapsules are entirely composed of mucoadhesive polymer or have external layer with adhesive properties known as mucoadhesive microspheres. These efforts enhance intimate contact with the mucus layer and drug targeting to absorption site.

1.3 Mucoadhesive Drug Delivery System

The MDDS is a drug delivery system, which utilizes property of bioadhesion of certain water-soluble polymers which becomes adhesive on hydration & hence can be used for targeting a drug on a specific region of body for enhanced time period.

In a drug delivery the bioadhesion refers to the attachment of any drug carrier system to a particular biological location. It may include various biological surfaces like epithelial tissue and mucous coat on any surface of a tissue. If the adhesive attachment occurs at mucous coat, the phenomenon is known as mucoadhesion in which the delivery system is attached to the mucus membrane. The mucosal layers contains the gastrointestinal tract, the urogenital tract, the ear, nose & eyes.

2. Mechanism of Mucoadhesion



The mechanism of mucoadhesion is divided in two steps:

- The contact stage.
- The consolidation stage.

Contact stage – In this stage the mucoadhesive material comes into contact with mucous membrane, with speeding & swelling of formulation, to establish intimate contact with the mucous layer.

Consolidation stage – In this step the moisture activates the mucoadhesive material, and plasticizes it, allowing polymer chains to break and interact with mucus by weak bonds like van der waals and hydrogen bonds.

3. Mucoadhesion Theories

3.1 Electronic Theory

In this theory, the mucoadhesive as well as biological materials contains opposing electrical charges, when these materials come into contact they transfer electrons and forms electronic double electronic layer at interface, in which the mucoadhesion strength is determined by the attractive forces present within the electronic double layer.

3.2 Adsorption Theory

In Adsorption theory, the mucoadhesives stick to the mucus by secondary chemical interactions, like hydrogen bonds, van der waals, electrostatic attraction, or hydrophobic interactions.

3.3 Wetting Theory

The wetting theory is applied on the liquid systems which show affinity towards surface by spreading on it. Contact angle technique is used to measure the affinity. If the contact angle is lower, then its affinity is greater. If the contact angle is equal or close to zero, then it shows adequate spreadability.

3.4 Diffusion Theory

Diffusion theory describes the interaction of polymer and mucin chains at depth level to form a semipermanent adhesive bond. In this, the adhesion force increases with the degree of penetration of the polymer chains. Various factors affect on penetration rate like diffusion coefficient, mucoadhesive chains, and contact time.

3.5 Cohesive Theory

This theory includes the bioadhesion in which the intermolecular interactions occurs into similar molecules.

3.6 Mechanical Theory

Mechanical theory considers adhesion to be possible due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process.

4. Advantages of Mucoadhesive Microsphere Drug Delivery System

- A prolonged residence time at the site of drug action or absorption.
- Localization of drug action of the delivery system at a given target site.
- Ease of administration.
- Convenient termination of therapy. (Except GIT)
- Permits localization of the drug to the oral cavity for a prolonged period of time.
- Can be administered to unconscious patients, except
- Offers an excellent route for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
- Facilitation in achieving a significant reduction in dose thereby reducing dose related side effects.
- Offers a passive system of drug absorption and does not require any activation.
- Drugs which show poor bioavailability via the oral route can be administered conveniently.
- Rapid systemic absorption.
- The presence of saliva ensures a relatively large amount of water for drug dissolution unlike in case of rectal & transdermal routes.

- Provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents, etc.

- The buccal mucosa is highly perfused with blood vessels & offers a greater permeability than the skin, with less dosing frequency & shorter treatment period.

5. Disadvantages of MMDDS

- Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste and odour and cannot be administered by this route.

- Drugs which are unstable at buccal pH cannot be administered by this route.

- Only drugs with small dose requirements can be administered.

- Drugs may be swallowed with saliva and lose the advantages of buccal cavity route.

- Only those drugs which are absorbed by passive diffusion can be administered by this route.

- Eating and drinking may become restricted however swallowing of the formulation by the patient may be possible.

- Over hydration may lead to the formation of a slippery surface and the structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.

6. List of Mucoadhesive Polymers

NATURAL	SYNTHETIC
Gelatin	Methyl cellulose
Pectin	Ethyl cellulose
Guar gum	Polyvinyl alcohol
Tragacanth	Polycarbophil
Lecithin	Polyethylene oxide
Sodium alginate	Polyacrylic acid
Karaya gum	Esters and Halides
Soluble starch	Carbomers
Chitosan	Hydroxy ethyl cellulose (HEC)
Locust bean gum	Hydroxy ethyl cellulose (HPC)
Xanthan gum	Sodium carboxymethyl cellulose (NaCMC)
Carrageenan	Poly hydroxy ethyl methyl acrylate

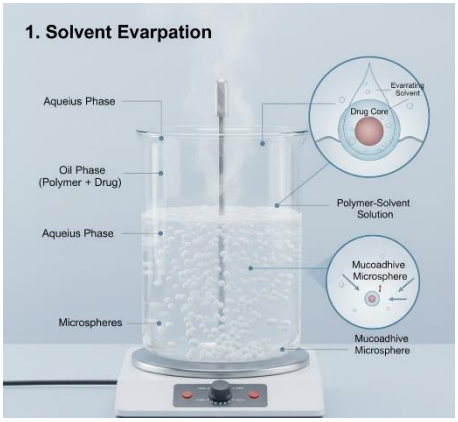
7. Ideal characteristics of Polymers

- The polymers should not be irritant to mucous membrane.
- It should create a strong non-covalent bond with mucin-epithelial cell surfaces.
- It should adhere tissues fastly & must be specific to sites.
- It should not absorbed through GI tract.
- It should be easily administered with drug & should not prevent its release.
- It should be cost effective and its methods also.
- It should not be breakable during storage and shelf life of dosage form.
- The polymer and product after degradation should not be harmful.
- More effectiveness is shown by cationic & anionic polymers than neutral polymers.
- Carboxymethylcellulose, gelatin, hyaluronic acid, viz Carbapol, polycarbophil all have high binding polymers.

8. Methods of Preparation

8.1 Solvent Evaporation

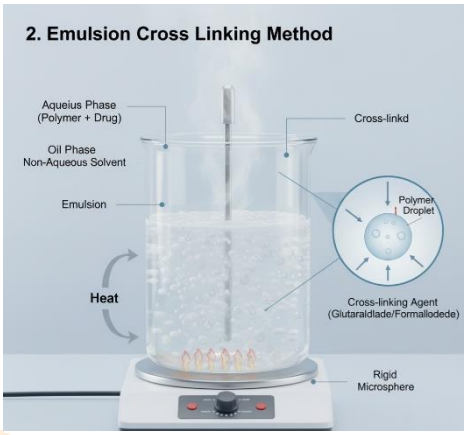
The mucoadhesive microspheres are manufactured from by using solvent evaporation technique, which involves the formation of an emulsion between polymer-containing organic phase (oil phase) and immiscible continuous phase (aqueous phase). The water soluble or water insoluble core material is either dissolved or dispersed in polymer/solvent solution. Then this mixture is agitated in the continuous phase to form droplets of required size, creates an emulsion, like an oil-in-water (o/w) type, or by the help of surfactant like polyvinyl alcohol (PVA) which stabilize it. The evaporation of the volatile organic solvent is done by heating, vacuuming or continuous stirring which leads to precipitate and shrink of polymers around the core material. The matrix-type microsphere is formed by dissolving core material into polymer solution. The microspheres are separated from liquid medium by removal of solvent, and then cleaned & dried.



8.2 Emulsion Cross Linking Method

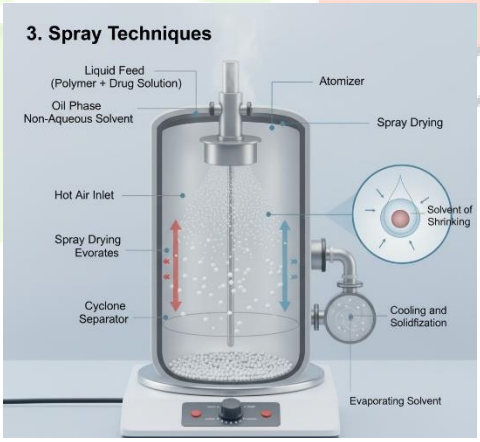
In this method, firstly the natural polymers are mixed into water to create an aqueous phase, then it dispersed into a non-aqueous (oil) phase. In second step it involves the cross-linking of dispersed droplets, this is carried out by applying heat or by introducing chemical cross linking agents like glutaraldehyde or formaldehyde. The whole process is carried out in a liquid manufacturing vehicle. The microcapsule coating material is dissolved in a volatile solvent that can not mixed with liquid manufacturing vehicle.

The core material is either dissolved or dispersed within coating polymer solution, then it dispersed in liquid vehicle to encapsulate core material.



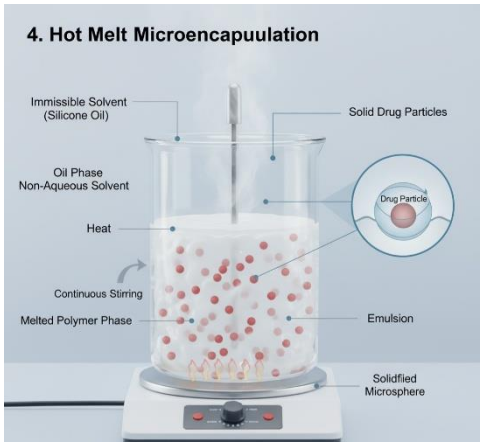
8.3 Spray Techniques

Spray based techniques involves both spray drying and spray congealing to prepare microspheres (particles between 1 – 100 um) based on drying of medicine & polymer in air. Firstly the polymer is dissolved in organic solvent like acetone, dispersed the drug in the solution by homogenization and then atomizing the mixture into fine mist. Cyclone separator is used. (Microspheres are separated by using cyclone separator and remaining solvent removed by the vacuum drying). In spray drying, the prepared mist is sprayed into a hot air stream, the solvent evaporates & microspheres are remained. The spray congealing involves spraying of droplets into a cool environment which cause cooling of polymer. Both batch and large scale manufacturing is done by this method.



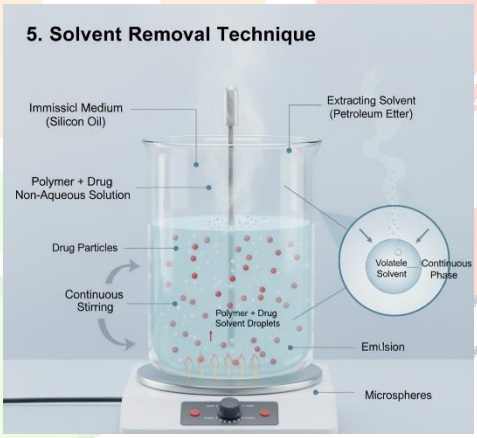
8.4 Hot Melt Microencapsulation

Hot melt microencapsulation is a technique where solid-drug particles are directly dispersed into a melted polymer. Then, this mixture is suspended in an immiscible solvent (like silicone oil), slightly heated slightly above the polymer's melting point and stirred continuously to form an emulsion. When the emulsion stabilizes, allow to cool it to solidify the polymer, leads to formation of microspheres ranging from 1 – 1000 um in diameter. The size of particles can be controlled by adjusting the speed of stirring.



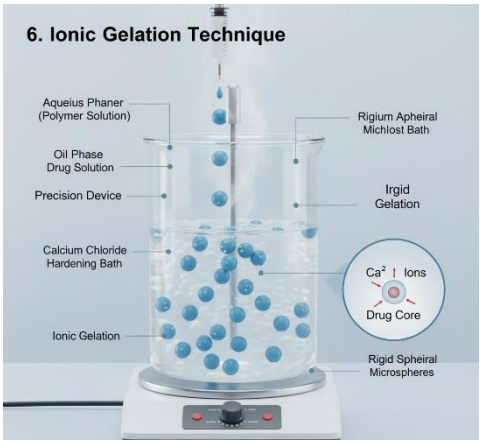
8.5 Solvent Removal Technique

This is an effective non-aqueous microencapsulation method useful for water sensitive polymers, like polyanhydrides, because the complete process occurs at room temperature in organic solvents, without any aqueous solutions. In this technique the polymer dissolved in a volatile organic solvent (like methylene chloride), drug is dispersing into this solution and them suspending this mixture in an immiscible medium like silicon oil containing span 80 and methylene chloride. The petroleum ether is used as extractant to draw methylene chloride out of oil and form microspheres. Then filtered, washed and dried under vacuum. This technique minimizes drug loss and effective for hydrophilic materials, which show similar theoretical and actual drug loading.



8.6 Ionic Gelatin Technique

This technique involves preparing a viscous dispersion of the drug within a homogeneous polymer mixture, containing sodium alginate and a mucoadhesive polymer in purified water. Then, this mixture is sprayed into a 10\% w/v calcium chloride solution, where the sodium alginate immediately cross links or cause ionic gelation to form rigid spherical microspheres. After 15 minutes separate out the microspheres and washed repeatedly with water to remove calcium residue and lastly dried at 450 C for 12 hours.



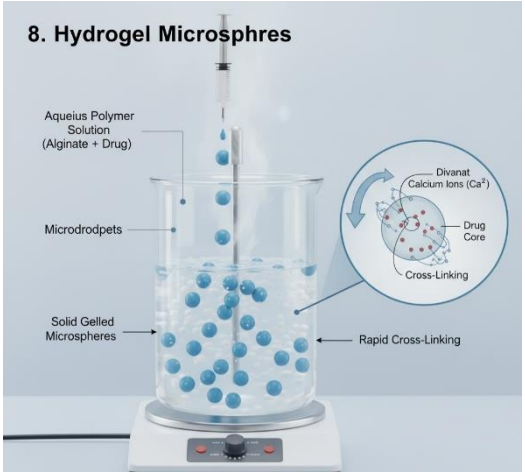
8.7 Phase Separation Coacervation Technique

In this technique, drug particles are suspended within a polymer solution. On the addition of an incompatible second polymer, encapsulation initiates, which forces the primary polymer to phase separate and engulfs the dispersed drug particles. A non-solvent is added to solidify the polymer shell. Throughout this process the

suspension must be continuously stirred to prevent the newly formed microparticles from agglomeration.

8.8 Hydrogel Microspheres

Hydrogel microspheres are also made of alginate and for an all-aqueous system that avoids residual solvents. In this method, active ingredient suspended in an aqueous polymer solution is extruded through a precision device to form microdroplets. These droplets fall into a gently stirred calcium chloride hardening bath, where the divalent calcium ions rapidly cross-link the polymer chains, to form solid gelled microspheres.



9. Evaluation

9.1 Yield of Microspheres :-

Calculates the percentage recovery of prepared microspheres.

Yield (%)= Actual weight of product / Total weight of excipients & drug

9.2 Entrapment Efficiency

Prepared microspheres are crushed are dissolved in distilled water with stirring, filter and assayed by UV spectrophotometer. It measures the ratio of the actual amount of drug in microspheres to the theoretical amount of drug.

9.3 Particle size determination

The average particle size of the microspheres is measured by using optical microscope (10 \times eye piece \& \ 45 \times objective) \& measuring 100 particles using a calibrated colorimeter.

9.4 Bulk density

The bulk density is measured by using the tap method by measuring the volume occupied by a known weight of microspheres in a graduated cylinder after tapping.

9.5 Swelling Index

Determines the capacity of mucoadhesive microspheres to swell by absorbing liquid to cause mucoadhesion.

Percent swelling = (DT – D0 /D0) × 100

Where, D0 = dry weight. DT= expanded weight.

9.6 In-vitro Drug Studies (Dissolution)

Measures the rate and amount of drug release over time using a USP Apparatus Type-I (basket), carried out in two steps. The dissolution medium contains 0.1N HCl for first 2 hours followed by phosphate buffer at pH 6.8, and analyzed the samples by UV-spectrophotometry at 202 nm.

9.7 In-vitro Diffusion Studies

It determined the drug permeation across a membrane – sheep nasal mucosa using a nasal diffusion cell . During the process, samples are withdrawn at intervals and analyze the drug content by UV spectrophotometry

10. Applications of Mucoadhesive Microspheres

- Mucoadhesive microspheres drug delivery system is useful for oral, buccal, sublingual, mucosal, nasal, GI tract, topical, vaginal, rectal, and vascular routes for local and systemic effects.
- Microspheres are used to form controlled and sustained release of drugs.
- Microspheres are used to prepare enteric coated dosage forms.
- Microspheres can reduce volatility because the encapsulated material stored for extended time period.
- Microspheres are involved in creation of IUCDs for controlled local delivery.
- Radioactive microspheres are used for imaging liver, lungs, bone marrow, spleen & other organs. Also used to image thrombi in thrombosis.
- Microspheres helps to reduce moisture absorbing characteristics of various materials.

- Most of preparations are prepared by using microspheres to lessen irritation to the gastric mucosa.
- The use of microspheres helps to reduce risks related to harmful substances.
- Microspheres containing drugs have defense against deterioration and protection from humidity, light, oxygen & heat.
- Mucoadhesive microspheres are employed to deliver drugs at specific site by improving drug bioavailability.

11.List of Novel Formulations using Mucoadhesive Microsphere

Sr.no	Drug Name	Therapeutic Use	Mucoadhesive Polymers used	Advantages of Microspheres
1.	Propranolol	Anti-hypertension	HPMC,Carbapol 934P, Sodium CMC.	Successfully designed for sustained release which improved overall patient compliance.
2.	Furosemide	Diuretics	Carbapol, Sodium alginate	Mucoadhesive microsphere formulation enhanced systemic bioavailability
3.	Nifedipine	Antihypertension	Carbapol, HPMC	Show excellent controlled release properties with high drug entrapment efficiency by using polymer combination
4.	Amoxicillin	Antipyloric for gastric and duodenal ulcer	Guargum, Sodium CMC, HPMC, Carbapol 940P	Enhanced eradication of H.pylori compared to standard suspension delivery
5.	Ranitidine	Gastroretentive	Sodium carboxymethyl cellulose, Chitosan	Successfully formulated the mucoadhesive microspheres of Ranitidine hydrochloride
6.	Simvastatin	Hypolipidemic	Sodium alginate, Sodium CMC, Carbapol 940P, HPMC	Microspheres of Simvastatin show release by a diffusion controlled kinetic mechanism
7.	Glipizide	Antidiabetic	Sodium alginate	Enhanced gastrointestinal residence time, and improved diabetes treatment
8.	Cephalexin	Treatment of respiratory infection	Guargum, Sodium alginate	Resulted in improved bioavailability and reduced required dose frequency
9.	Flurbiprofen	NSAID	Carbopol, , HPMC, Sodium CMC, Chitosan	Prolonged release, increased residence time in stomach (gastroretention)
10.	Insulin	Peptide	Chitosan, Polyacrylic acid (PAA)	Bypassing first-pass metabolism, enhanced peptide absorption
11.	Theophylline	Bronchodilator	Polyvinyl Alcohol (PVA), Carbopol	Bypassing first-pass metabolism, controlled release through the buccal mucosa
12.	Metformin	Antidiabetic	HPMC, Carbopol, Sodium Alginate	Controlled release for consistent glucose management
13.	Cefuroxime	Antibiotic	Chitosan, Eudragit	Increased absorption in the gastrointestinal tract

14.	Natamycin	Antifungal	Carbopol, Chitosan, \gamma-Cyclodextrin	Localized action, prolonged retention at the site of infection
15.	Sumatriptan Succinate	Migrane treatment	Sodium Alginate, PVP, Chitosan	Rapid absorption/onset of action through nasal route, sustained oral release.

12. Conclusion

Mucoadhesive microspheres drug delivery is an advanced drug delivery system. They have the ability to adhere to mucosal membranes which give pharmacological benefits like increased plasma drug concentration, extended residence time, improved bioavailability, and protection of drug from inner environment. Their main goal is to achieve the controlled drug release, leading to decreased drug concentration at non-sites target and allowing potent, effective delivery of the drug. Mucoadhesive demonstrates their future importance in optimizing drug therapy and patient outcomes.

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