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# REVIEW ON MUCOADHESIVE MICROSPHERE FOR CONTROLLED DRUG DELIVERY

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**ABSTRACT**

Microspheres play a significant role in the innovative medication delivery system because of their small size and effective carrying capacity. Microspheres' prolonged residence period allows for the coupling of bioadhesive properties, such as mucoadhesion, to create mucoadhesive microspheres. The current study is concerned with the review of bioadhesive or mucoadhesive microspheres for their combined effect of bio adhesion and the surface-to-volume ratio of microspheres with particle sizes ranging from 1-1,000m range in diameter and having a core of drug and outer layer of the mucoadhesive polymer due to their controlled and prolonged releases; microspheres are unique among all other substances. This review discusses the numerous types of microspheres, their preparation methods, and a fundamental technique to assess their efficacy. The most important highlight is microspheres in pharmaceutical applications using microspheres administered by various systemic routes, including oral, transdermal and parenteral. It has a high safety profile and is the perfect targeting mechanism. The information regarding mucoadhesion and mucoadhesion ideas is provided in this review article. Additionally, it lists several techniques for making mucoadhesive microspheres.

**KEYWORDS**

Mucoadhesion, Microspheres, Bioavailability and Polymers.

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## INTRODUCTION

The oral route is the most practical drug administration, with a high patient compliance rate. Modifying the GI transit time, typically 2-3 hours for gastric resistance, is one of the key tasks in creating sustained oral or controlled drug delivery systems. Inters Subjective variability and the fed/fasted condition of the stomach are terms that may apply depending on the individual[1]. In contrast to the medicine delivery mechanism, the word

novel seeks something fresh out of necessity. A medicinal chemical can be delivered to the target site using controlled and sustained release. Using microspheres as medication carriers are one such strategy[2]. Microspheres are described as tiny, insoluble, free-flowing spherical particles with sizes ranging from about 50 nm to about 2 mm and made up of a polymer matrix and medication[3].

## MUCOADHESION

The contact between a mucin surface and a synthetic or natural polymer is called mucoadhesion. Integrating mucoadhesive hydrophilic polymers with the active pharmaceutical ingredient in pharmaceutical formulations like "microspheres" has been widely touted as a method of attaining site-specific drug delivery (API)[4].

## MICROSPHERES

The use of microspheres as a drug carrier is one technique that can be used in a continuous controlled-release fashion. Small, spherical particles called microspheres have diameters in the micrometer range (usually 1m to 1000m). Microspheres are sometimes referred to as microparticles[5].

## MUCOADHESIVE MICROSPHERES

Microparticles and microcapsules with a diameter of 1 to 1000m that are either totally made of mucoadhesive polymer or have an exterior covering with adhesive properties are referred to as mucoadhesive microspheres. The possibility of using microspheres for controlled and spatial medication delivery[6].

## CLASSIFICATION OF POLYMERS

### Hydrophilic Polymers

These are the water-soluble polymers, such as chitosan, hydroxyethyl cellulose, hydroxypropyl methylcellulose, sodium carboxy methyl cellulose, carbomers, and plant gums, that expand indefinitely when in contact with water before completely dissolving[7].

### Hydrogels

These substances may swell in water and are typically cross-linked polymers with constrained swelling potential, such as carrageenan, sodium alginate, guar gum, and modified guar gum[8].

Thermoplastic Polymers

These polymers include semi-crystalline bioerodible polymers, such as polyanhydrides and polylactic acid, and non-erodible neutral polystyrene, which produce carboxylic acid groups when they break down. Polyvinyl alcohol, polyamides, polyethylene glycols, polyvinyl ethers, esters, halides, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and sodium carboxymethylcellulose are just a few examples of the synthetic polymers used in mucoadhesive formulations[9].

## SPECIFIC SITE-DIRECTED BIOADHESIVES-THE NEXT GENERATION

Site-specific chemical agents tethered to the polymeric DDS can target particular mucosal surfaces[10].

### Lectins

It can be characterized as non-immune proteins that selectively and non-covalently bind to carbohydrates. Lectins can improve medication penetration and promote the adhesion of microparticles to the intestinal epithelium[4].

### Bacterial Adhesions

Fimbriae allow bacteria to cling to the epithelial surfaces of the enterocytes.

Many bacterial strains have long, lectin-like proteins called fimbriae on their surface. Their presence has been linked to pathogenicity, such as when *Escherichia coli* adheres to the brush edge of epithelial cells through the K99 protein. *E. coli* enterotoxin synthesis and cellular absorption need the presence of fimbriae[11].

### Amino acid sequences

Protein Sequences When coupled to microparticles, some amino acid sequences can facilitate binding to particular cell surface glycoproteins because they have complementary regions on the surfaces of cells and mucosa. Which can be targeted by

complementary amino acid sequences connected to the drug delivery device, such as amino acids[12].

**Types of Microspheres**

**Bioadhesive / Mucoadhesive Microspheres**

Adhesion is the ability of a medicine to cling to the mucosal membrane when using water-soluble polymers 11, 12. Bio adhesion can be defined as the attachment of a medication delivery device to a mucosal membrane, such as the buccal, ocular, rectal, nasal, etc[13].

**Magnetic Microspheres**

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**Floating microspheres**

These are used to administer gastro-retentive drugs because their bulk density is lower than that of gastric fluid, which allows them to float freely in the stomach without slowing down the rate at which the stomach empties, which enhances stomach residence and heightens plasma concentration fluctuations[15].

**Radioactive Microspheres**

Radio embolism treatment occurs when microspheres larger than capillaries (10-30nm) come into contact with them; they tap into the first capillary bed.

**Polymeric Microspheres**

The many varieties of polymeric microspheres can be divided into synthetic polymeric microspheres and biodegradable polymeric microspheres[12].

**Biodegradable Polymeric Microspheres**

The idea behind using natural polymers like starch is that they are biodegradable, biocompatible, and naturally sticky. Biodegradable polymers prolong their residence when in contact with mucous membranes, causing gel formation[7].

**Synthetic Polymeric Microspheres**

In clinical applications, these microspheres can be employed as bulking agents, fillers, embolic particles, drug delivery vehicles, etc[5].

**Factors Affecting Mucoadhesion**[11]

Charge on the polymer
pH
Molecular weight
Swelling
Mucoadhesive polymers
Chitosan
Polyacrylic acid (PAA)
Pectin[1].

**Theories of Mucoadhesion**

Bio adhesion is a phenomenon that happens through a complicated method.

Numerous researchers have studied bio adhesion; nonetheless, dates six ideas have been put out to help us better understand the phenomena of adhesion and to help us comprehend how bio adhesion works among the theories[15].

According to the electronic theory, attractive forces are produced when electrons are transferred between surfaces, forming an electrical double layer.

According to the wetting hypothesis, there is a larger affinity between the liquid and the substrate surface if the contact angle of liquids on the substrate surface is lower[10].

According to the adsorption theory, the adhesive connection between the substrate surfaces is caused by intermolecular forces, specifically hydrogen bonds and Vanderwaal forces.

The diffusion hypothesis states that polymer chains on the substrate surface diffuse over the adhesive contact to form a networked structure[9].

The mucosa is mostly composed of >95% water and >99% mucin, with the remaining components being protein, lipids, and mucopolysaccharides[8].

## MECHANISM OF MUCOADHESION

**Mucous membranes**

The wet surfaces lining the various body parts' walls are called mucus membranes. Cavities like the respiratory and gastrointestinal (GI) tracts. Mucus which the goblet cells release. Mucus can be found as a coating of gel. Attached to the mucosal surface, hanging, or in the shape of a luminal Soluble. All mucus gels' primary ingredients are mucin

glycoprotein, lipids, inorganic salts, and water. The mucus acts as a shield. Lubricant and barrier as well[3]. Structure of the mucus membrane is depicted in Figure No.1.

The mucosal layer, lined by goblet cells, lines the gastrointestinal tract and serves as a lubricating and protecting barrier for the mouth, nose, and vaginal cavity. The mucins, which are heavily glycosylated big molecules that form a negative charge at physiological pH 7.4, gives mucus its mucoadhesive qualities. These theories include the electrical theory and the wetting theory. The two stages of adhesion are wetting and mucoadhesion. Wetting happens when a polymer is exposed to mucus and comes into close contact with the mucosal surface, which is necessary for mucoadhesion[8].

When the polymer is dehydrated and is applied to the mucosal surface, the consolidation stage was mucoadhesive strength is stronger. The mucosal layer, once dry, transforms from having lubricating characteristics to sticky capabilities. The polymer will start to absorb the moisture from the mucosal layer[5]. Mechanism of mucoadhesion is observed in detail in Figure No.2.

**Characteristics of an ideal mucoadhesive polymer**

It shouldn't irritate the mucous membrane in any way[11].

The mucin-epithelial cell surfaces should ideally form a potent noncovalent bond with it[1].

It should be simple to include in the medicine and shouldn't prevent its release[12].

It should make it simple to incorporate the treatment and shouldn't prevent its release[13].

The polymers must not break down while stored, or the dosage form is kept on the shelf[14].

## POLYMERS USED FOR MUCOADHESIVE MICROSPHERES

The polymers that make the mucoadhesive microspheres impact their characteristics, including surface features, mucoadhesion force, drug release pattern and clearance. Solvable and insoluble, non-biodegradable and biodegradable polymers can all be employed to create mucoadhesive microspheres. These can be natural or artificial polymers, hydrogels or thermoplastics, homopolymers, copolymers, or mixes[14].

**Methods of Preparations**

Various methods are available to prepare the mucoadhesive microspheres according to the various publications. Some are enlisted in this review.

**Phase separation coacervation technique**

This development will adopt the principle of decreasing the polymer's solubility in the organic phase to signal the formation of a polymer-rich phase known as the coacervates. Addition of non-solvent effects during the polymer's solidification. Since there is no clearly defined state at which equilibrium is reached, the process variables are crucial since they regulate the kinetics of the produced particles[8].

**Emulsion cross-linking method**

This approach involves dissolving the medication in an aqueous gelatin solution heated for an hour at 40°C. The combination is stirred at 1500rpm for 10 minutes at 35°C while the key is added drop wise to the liquid paraffin. If there is no emulsion, the mixture is stirred for 10 minutes at 15°C. Finally, they are treated with 100 ml of 10 mm glycine solution containing 0.1%w/v of tween 80 at 37°C for 10 minutes to block unreacted glutaraldehyde Gelatin microspheres is an illustration of this approach[13].

**Solvent Evaporation**

The operations are performed in a liquid manufacturing machine. The liquid manufacturing vehicle phase and the volatile solvent to spread the microcapsule coating are incompatible. The solvent is then removed from the mixture if necessary, allowing the polymer of the core material to dissolve in the polymer solution and shrink around the core. In solvent evaporation, whether aqueous (o/w) or non-aqueous emulsion is between a polymer solution and an immiscible continuous phase. The contrast between microcapsules made of hyaluronic acid and gelatin and mucoadhesive

microspheres of hyaluronic acid, chitosan glutamate and a combination of the two[11].

**Spray drying**

The polymer is first dissolved in a suitably volatile organic solvent, such as dichloromethane, acetone, etc., before being dried using spray technology. The medication is subsequently dissolved in the polymer solution and homogenized quickly. Then, a jet of hot air is used to atomize this dispersion. The disintegration produces tiny droplets or a fine mist, from which the solvent instantly evaporates, creating microspheres with a size range of 1-100m. A cyclone separator removes microparticles from the hot air, and any remaining solvent is removed before vacuum drying. Rapidity in this process causes the development of porous microparticles[10].

**Ionic gelation**

This method created an alginate/chitosan particulate system for diclofenac sodium release. This approach involves adding the medication to a sodium alginate aqueous solution. Stirring is kept until the mixture is complete, then it is dropped gradually into a Ca2+/Al3+ solution. After being left in the original key for 24 hours, the internally qualified microspheres were separated by filtration. The full release is achieved between pH 6.4 and 7.2, but the drug won't release at an acidic pH[10].

## EVALUATION PARAMETERS

After the preparation of mucoadhesive microspheres to know about the safety, efficacy of the optimized formulation, the following evaluation parameters are useful.

**Particles' size**

Optical microscopy will be used to make the determination[3].

**Percentage yield**

A method's efficiency will be determined by computing the percentage yield. As a result, it aids in choosing the best production method[13].

%Yield Total microparticle weight

Total polymer weight = 100

Bulk density

The ratio between the mass of an untapped powder sample and its volume, which includes the contribution of the inter particulate void spaces, is the bulk density of a powder. The bulk density is measured in grams per milliliter (g/ml)[7].

Bulk density (ρb) = W/Vb

Where w is the weight of the sample in grams, Vb is the final bulk volume of granules in cm 3

**Tapped density**

The powder sample was contained in a container mechanically tapped to enhance the bulk density, known as the tapped density. The tapped density is produced.

To get the ongoing reading, tapping is continued further. Finally, the following equation can be used to calculate tapped density[1].

Tapped density (ρt) = W/ Vt

**Mucoadhesion test**

Using an *in-vitro* wash-off test, the microspheres' mucoadhesive qualities are assessed. A glass slide (3inches by 1inch) had a piece of rat stomach mucosa (3cm by 1cm) connected to it with thread. The dissolving test device was set up so the tissue sample was regularly moved up and down in a beaker filled with the simulated stomach fluid USP (pH 1.2). The number of microspheres that remained attached to the tissue was counted after 30 minutes, 1 hour and hourly intervals up to 10 hours[3].

**Degree of swelling**

The degree of swelling demonstrates the mucoadhesive microspheres' capacity to swell at the absorbent surface by absorbing. Fluids present there, which is a crucial condition for the beginning of mucoadhesion. Polymer volume change (Wg Wi) can be used to calculate the degree of swelling[2].

Degree of swelling W = WI g- W g ×100

Where, Wi - Initial weight of microspheres

Wg - Final weight of microspheres.

**Limitation**

Compared to ordinary formulations, the costs of the components and processing for controlled release preparations are significantly greater[5].

How polymer matrix decays and how it affects the environment.

What happens to polymer additives such as fillers, stabilizers, antioxidants, and plasticizers?

There is less reproducibility[5].

**ADVANTAGES OF MUCOADHESIVE MICROSPHERES DRUG DELIVERY SYSTEM**

Easily localized in the area and used to increase and improve drug absorption. For instance, gentamycin, insulin, dopamine, vasopressin, testosterone and its esters, etc[2].

Promote close contact between the formulation and the subsurface of absorption. This enables the alteration of tissue permeability for protein and peptide absorption, among other macro molecules[12].

Extend the dosage form's period in residence at the application and absorption sites to enable once- or twice-daily dosing[11].

**DISADVANTAGES OF MUCOADHESIVE MICROSPHERES DRUG DELIVERY SYSTEM**

**The formulas' release may be altered**[5]

Different circumstances, such as meals, the speed at which it travels through the stomach, the pace at which mucin turns over, etc., may affect the release rate.

There are variations in the release rate from one dose to the next[6].

**Applications of microspheres**

**The following list of applications for microspheres is detailed**

Enteric-coated dose forms can be made using a microsphere, allowing the medication to be selectively absorbed in the intestine rather than the stomach.

Encapsulation has been used to separate incompatible compounds, such as medicinal eutectics.

Dosage formulations with controlled and sustained release

Using a microsphere can reduce volatility[11]

Microspheres have also been utilized to reduce the risk of handling hazardous or poisonous materials

Several medications have been microencapsulated to decrease gastric annoyance.

A microsphere preparation technique for intrauterine contraceptive technology[13].

**CONCLUSION**

In contemporary pharmaceutical formulations, interest in novel drug delivery mechanisms has grown significantly. Because they transport the medicine to a specific spot for a longer period, mucoadhesive microspheres are a potential technique in the controlled delivery of drugs to a particular site. The mucoadhesive microspheres can be employed for targeted medication delivery to specific body regions, as well as for controlled release and increasing bioavailability. A mucoadhesive delivery device has wide scope in the future administration of various drugs with improved adhesion and successive sustained delivery of drug throughout the gastrointestinal tract.

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**CONFLICT OF INTEREST**

We declare that we have no conflict of Interest.

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