MUCOADHESIVE MICROSPHERES: CURRENT CHALLENGES AND FUTURE PROSPECTS - A REVIEW

Stanley Dinesh[1], Gayathri. H[2*], Damodharan. N[3]

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Abstract

Drug delivery by fusing the medication to a carrier particle such as liposome, mucoadhesive microsphere, nanoparticle, etc. Drug delivery through mucoadhesive microsphere plays a major role in novel method of drug delivery. Due to their effective qualities like small size, sticking nature to the mucosal surface and release the medicine over an extended period of time, mucoadhesive microspheres improve drug absorption. Emulsion cross-linking, single emulsion, ionotropic gelation, phase inversion, spray drying, solvent removal, and hot melt techniques can all be used to generate these systems. These mucoadhesive devices can protect the drug both during transit to the delivery site and throughout absorption. This review provide an overview of the many mucoadhesive microsphere components that depend on various polymers, as well as their preparation, evaluation, advantages, disadvantages and drug delivery applications.

[1,2*,3]SRM College of Pharmacy, SRMIST, Kattankulathur campus, Tamil Nadu, India
Email: gayathrh@srmist.edu.in

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1. Introduction

Numerous epithelial surfaces are covered in mucus, a viscous and diverse biological substance. Mucus-secreting cells can be found all over the body, although they are most prevalent in the nasal, ocular, and buccal regions as well as the gastrointestinal, reproductive, and respiratory tracts. Mucus serves as a protective barrier against hazardous chemicals and as a lubricant to lessen shear pressures and also it serve additional crucial purposes(1).

Up to 95% of mucus is made up of water, while 15% is made up of inorganic salts. Less than one each of lipids, carbohydrates, and glycoproteins, with a maximum weight of 5%. The branched-oligosaccharide chains that are connected to the protein core of mucus glycoproteins, also known as mucins, extend for 63% of their length.

Mucoadhesion is the occurrence of natural or artificial polymers sticking to a mucosal surface. The creation or advancement of mucoadhesive materials depends on an understanding of the forces and mechanisms that lead to a successful bond between polymer and mucous layer. Some polymeric hydrogels have mucoadhesive characteristics. High levels of hydrogen-bonding chemical groups, such as hydroxyls and carboxyls, anionic surface charges, high polymer molecular weights, high polymer chain flexibility, and surface tensions that encourage spreading into the mucus are just a few of the traits that have been shown to increase hydrogel mucoadhesive properties.

The three phases that make up the process that causes the mucoadhesion phenomena are broadly accepted

1] The polymer should be able to make direct touch with the tissue after being wet and swelling.

2] The polymer chains interacting with each other and becoming entangled with the mucin chains.

3] There should be the potential of weak chemical bonding. The wetting hypothesis defines how a mucoadhesive polymer distributes across a tissue and used in liquid and semisolid mucoadhesive systems. According to this theory, surface tensions at the interfaces are used to calculate the spreading coefficient, which stands in for the polymer's mucoadhesion properties. The force required to separate the polymer surface is examined by the fracture hypothesis(1). Since the early 1980s, many techniques have been developed to assess the prospective mucoadhesive characteristics of novel polymeric materials. Numerous strategies for malliesim evaluation have been developed as a result of the physical variety of the mucoadhesive devices that have been created. Many of the methods that can be found in the literature are based on the measurement of the force necessary to separate a mucoadhesive substance from a biological membrane(2). Peel, shear, and tensile forces can all be determined depending on how the mucoadhesive material breaks from the biological surface. When testing mucoadhesive products for transdermal or buccal applications, peel forces are assessed. One of the most impressive techniques for shear strength tests is the Wilhelmy plate method created by Smart et al. In this method, a glass plate covered in the mucoadhesive material to be evaluated is dipped into a mucin solution. The object holding the mucoadhesive substance is dragged out from the mucin solution, and the forces produced by surface tension on the plate are measured using a microbalance attached to the plate(2). Staining methods have also been used to assess mucoadhesive polymers. Using a hydrogel surface and mucin gold conjugates, Park's colloidal gold staining technique produced a red color. A direct-staining method has recently been proposed to evaluate a polymer's adherence to human buccal cells.

Some of the authors have discussed about the research studies of mucoadhesive microspheres. Canan Hascicek a, Nursin Gonul a,*, Nevin Erk b were made a microsphere formulations to enable nasal mucosal absorption of a highly polar medication. Gentamicin sulphate (GS) was chosen as a model drug for this experiment and was incorporated into the microsphere formulations at various drug/polymer ratios. The spray drying method was used to prepare the microspheres. In order to extend the residence time of the microspheres on the mucosa, hydroxypropyl methylcellulose was utilised as a mucoadhesive polymer in the formulations. For the formulations to increase the absorption of GS through nasal mucosa, sodium cholate was added(3). The microspheres' in vitro properties were identified. The particle size and production yield of the microspheres were assessed. Interaction of the medication with the drug polymer, mucoadhesive property, efficacy of the drug encapsulation, shape and surface properties, in vitro drug release, and viability for nasal drug delivery(3). Elisabetta Gavini1, Giovanna Rassu1, Tone Haukvik2, Cristina Lanni3, Marco Racchi3, & Paolo Giunched were developed the Mucoadhesive microspheres carrying cyclodextrins as nasal delivery devices for brain targeting in order to investigate cyclodextrins' capacity to inhibit the development of b-amyloid fibrils in vitro. Eight samples of microspheres containing chitosan, alginate, and either b-cyclodextrin or hydroxypropyl-b cyclodextrin in two different cyclodextrin to polymer ratios were produced by spray drying. The results show that no CD that has been tested has ever directly harmed cells, and they also show that cells are protected from b-peptide. The created microspheres have small particle sizes,

the ability to hold water, and the power to reduce the rate at which cds dissolve in vitro. Additionally, the compositions are thought to have strong ex vivo mucoadhesive properties. The amount of cyclodextrin, the percentage of cyclodextrin to polymer, and the type of polymer all have an impact on the properties of the microsphere. The alginate formulation with a greater cyclodextrin concentration clearly shows the best performance(4). Marta Szekalska1, Aleksandra Amelian, Katarzyna Winnicka were created ranitidine (RNT)-infused alginate (ALG) microspheres using the spray drying technique. The characteristics of the obtained microspheres included zeta potential, drug loading, surface shape, entrapment effectiveness, and particle size. The three different types of sticky layers employed to assess the mucoadhesive properties using a texture analyzer were gelatine discs, mucin gel, and porcine stomach mucosa. Microspheres displayed a smooth surface, a limited particle size range, and up to 70.9% RNT loading. According to first-order kinetics, all formulations displayed delayed drug release and had mucoadhesive qualities. There was no interaction between RNT and ALG, according to DSC reports. With a lengthy residence time in the stomach, designed microspheres are possible ranitidine carriers(5).

Jayvadan K. Patel,1 Rakesh P. Patel,1 Avani F Amin,2 and Madhabhai M. Patel1 were develop and thoroughly assess the mucoadhesive microspheres of glipizide's in vitro and in vivo performance. Chitosan-containing glipizide microspheres were created utilising a straightforward emulsification phase separation procedure and glutaraldehyde as a cross-linking agent. According to preliminary trial findings, the cross-linking agent volume, time, polymer to drug ratio, and rotation speed all had an impact on the properties of microspheres. Microspheres were free-flowing, spherical, and distinct. In the in vitro wash-off test, the microspheres demonstrated as better mucoadhesive property and a high percentage of drug entrapment effectiveness. The most effective batch had a swelling index of 1.42 percent and an excellent mucoadhesion of 78% after one hour. Additionally, the medication release lasted for more than 12 hours. The dependent variables were more significantly impacted by the polymer-to-drug ratio(6). The mucoadhesive microspheres were tested in vivo on albino Wistar rats, and the results showed that glipizide significantly reduced blood sugar levels(6).

Sanjay Patil1 , Anil Babbar2 , Rashi Mathur2 , Anil Mishra2 , and Krutika Sawant1 were create and characterise carvedilol (CRV) chitosan mucoadhesive microspheres for nasal administration to increase bioavailability for the treatment of hypertension and angina pectoris. The emulsification-cross-linking process was used to create the microspheres, which were then analysed using differential scanning calorimetry (DSC), X-ray diffraction (XRD), entrapment efficiency (EE), in vitro mucoadhesion, and in vitro drug release. Freundlich and Langmuir adsorption isotherms were also used to analyse the mucoadhesive characteristics. Testing was done in vivo on rabbits. The microspheres were 20–50 m in diameter and spherical, making them ideal for intranasal absorption. The percentage of mucoadhesion ranged from 74% to 88%, while the EE was seen in 42% to 68% of cases. It was discovered that mucin and chitosan microspheres had a significant connection, which helped to explain how electrostatic contact caused adsorption. In 8 hours, the microspheres released around 75% of the medication. Studies using DSC and XRD showed that CRV was molecularly distributed. The absolute bioavailability was high (72.29%), and the absorption rate was quick. Gamma scintigraphy showed that the microspheres left the nasal cavity gradually. It was determined that CRV might be delivered using chitosan microspheres after being administered nasally to increase bioavailability(7).

Rita J. Majithiya and Rayasa S. Ramchandra Murthy were create mucoadhesive clarithromycin microspheres based on chitosan to enable prolonged contact time for antibiotic drug delivery to treat stomach ulcers. In vitro performance of a mucoadhesive formulation based on microspheres was thoroughly assessed and characterised, and then rat in vivo pharmacokinetics were examined. By using glutaraldehyde as a crosslinking agent and an emulsification process, microspheres were created. The formulation and manufacturing conditions were optimized for % drug entrapment and mucoadhesion by modifying a number of formulation and process parameters, which included the amount of drug to polymer, the amount of the crosslinking agent, and the length of the crosslinking. The produced microspheres underwent extensive testing for particle size, percent drug entrapment, swelling kinetics, in vitro mucoadhesion utilizing rat stomach membrane, and in vitro drug release. To ascertain diffusion characteristics and drug retention in the stomach membrane of the formulation and the plain medication, in vitro permeation investigations across the rat stomach membrane were conducted. Finally, pharmacokinetic experiments in albino rats were used to assess the in vivo performance of the microsphere formulation in contrast to the plain medication. Up to 74% drug entrapment was achieved. According to swelling experiments, the ability to swell diminished as cross-linking levels rose. The degree of cross-linking and concentration of chitosan were found to be related in the in vitro drug release and in vitro mucoadhesion tests. In

contrast, polymer concentration showed a negative association with drug release while having a linear relationship (up to 86%) with mucoadhesion. The extent of cross-linking also showed an inverse correlation with drug release rate. When these results were analysed, the AUC 0 values for the microsphere formulation of clarithromycin and the plain drug suspension were 91.7 (g h/ml) and 24.9 (g h/ml), respectively. The study showed that there was better drug accumulation in the stomach membrane and that the microspheres had good mucoadhesion with the mucosa of the stomach. Additionally, microspheres showed prolonged drug release. So in theory, chitosan microspheres could be effective mucoadhesive drug delivery devices for the treatment of stomach ulcers with clarithromycin(8).

Siddra Khalid [a], Ghulam Abbas [b], Muhammad Hani f [a], Shahid Shah SyedNisarHussain Shah [a], Aamir J alil [d], Muhammad Yaqoob [d], Nabeela Ameer [a], Aye sha Anum [a] Inhibiting P-glycoprotein (P-gp) efflux and boosting natural polymer mucoadhesion can both enhance the absorption of BCS III medicines. Thiolated sodium alginate (TSA) was created in the current work by esterifying sodium alginate (SA) with thioglycolic acid (TGA). The thiol group was quantified using the Ellman's assay, and any S S connections were verified using the di-sulphide bond test. The thiol group of TSA was determined by FTIR, DSC, XRD, 1H NMR, and charring point. Viscoelasticity properties and the mucoadhesion with the rabbit gut were carried out following compression of 30 mg TSA tablets, which proved the gel-like rheological qualities with pig mucus. Thiol group concentration in the polymer ranged from 320 to 730 mol/g. The FTIR spectrum of TSA revealed a distinctive peak of the sulfhydryl group at 2557 cm1, and the decrease in the charring point from 220 °C to 178 °C was evidence that TSA had undergone thiolation. Mucoadhesion and edema were found to be directly correlated with the concentrations of TGA and SA, respectively. The produced microspheres have excellent rheological characteristics, a size range of 2 to 7 micrometers, and non-fickian drug release behavior(9).

Shazia Akram Ghumman a,□, Sobia Noreen b,c , Sidra tul Muntaha a were studied the creation, evaluation, and optimisation of Linum usitatissimum mucilage (LSM), a sustained release dosage form made using the ionic gelation technique, are the subjects of this study. LSM contains sodium alginate mucoadhesive microspheres loaded with metformin hcl. In vitro drug release for 12 hours and the impact of adjusting the polymer ratio with the medication were evaluated. All formulations had drug entrapment efficiencies that ranged from 77.93 3.67 to 92.25 4.08%, with sustained releases between 80 0.12% and 88 0.33% over a period of 12 hours. The super case II transport mechanism matched the Korsmeyers Peppas model (R2 = 0.9786-0.9964). All formulations had microspheres that ranged in size from 817-911 m on average. SEM and FTIR analysis were also performed, and ph of the buffer media had an impact on the swelling behaviour of the microspheres. In a wash-off test, these microspheres also demonstrated good mucoadhesivity. Metformin hcl-containing optimised LSM-alginate mucoadhesive microspheres significantly reduced blood sugar levels in diabetic rats over an extended length of time(10). Punam Gaba a , Sarbjot Singh b,1 , Monika Gaba a,*,1 , G.D. Gupta were studied a complex condition with polygenic origins, type 2 diabetes mellitus comprises both impaired insulin secretion and peripheral insulin resistance. Post-meal hyperglycemic spikes have been linked to higher cardiovascular mortality in type 2 diabetics, according to studies. In the past ten years, there has been a surge in interest in managing postprandial glucose excursions, leading to the discovery of numerous new drugs that specifically target postprandial hyperglycemia.Oral sulfonylureas continue to be a mainstay of therapy despite the availability of novel medicines for the treatment of type 2 diabetes mellitus because they are generally affordable and well tolerated.However, one significant risk factor needing hospitalisation with sulfonylureas is hypoglycemia, which is a major safety concern.A second-generation sulfonylurea having powerful, quick-acting, short-acting, and well-tolerated properties, glipizide lowers postprandial glucose levels. However, the use of glipizide for the treatment of type 2 diabetes mellitus is always accompanied with the risk of postprandial hypoglycemia and post-meal glucose excursions, if the dose is missed before to the meal. Since the stomach is where glipizide is absorbed, dosage forms that are held there via mucoadhesion would boost absorption, improve therapeutic efficacy, and reduce the amount of medication needed. Using the mucoadhesive polymer galactomannan, microsphere carrier systems are created(11).

Future prospects of mucoadhesive microspheres

The future prospects of mucoadhesive microspheres hold immense potential in various areas of biomedical research and drug delivery. Here are some key aspects that showcase their promising future:

Enhanced Drug Delivery: Mucoadhesive microspheres can improve drug delivery by providing sustained and controlled release of therapeutic agents. They can be designed to adhere to mucosal surfaces, such as those found in the gastrointestinal tract, respiratory system, and ocular tissues. This targeted delivery approach improves drug bioavailability, reduces side effects, and enhances patient compliance (12).

Localized Therapy: Mucoadhesive microspheres offer the advantage of localized therapy. By adhering to specific mucosal surfaces, they enable the direct and targeted delivery of drugs to the site of action. This is particularly beneficial in treating diseases such as oral infections, gastrointestinal disorders, respiratory conditions, and vaginal infections (13-15).Vaccine Delivery: Mucoadhesive microspheres have shown promise in vaccine delivery. They can be engineered to encapsulate antigens and adjuvants, facilitating the controlled release and prolonged exposure of these immunogenic components to mucosal surfaces. This approach holds great potential for developing effective mucosal vaccines against respiratory infections, sexually transmitted diseases, and other mucosal pathogens (16-18). Bioadhesion and Mucus Penetration: Advances in the development of mucoadhesive microspheres aim to enhance their bioadhesive properties and mucus penetration capabilities. By improving their interaction with the mucosal surface and overcoming mucus barriers, these microspheres can achieve prolonged residence time, increased retention, and enhanced drug absorption (19-21). Combination Therapies: Mucoadhesive microspheres can be used for combination therapies, where multiple drugs or therapeutic agents are delivered simultaneously. By incorporating different drugs or active agents into a single microsphere formulation, it is possible to achieve synergistic effects, optimize therapy, and simplify treatment regimens (22). Nanotechnology Integration: The integration of nanotechnology with mucoadhesive microspheres opens up new avenues for drug delivery and therapeutics. Nano-sized mucoadhesive microspheres can enhance cellular uptake, intracellular delivery, and target specific sites within mucosal tissues. This integration offers opportunities for advanced drug delivery systems, diagnostics, and personalized medicine (23).
Biomedical Applications: Mucoadhesive microspheres have potential applications beyond drug delivery. They can be utilized for mucoadhesive coatings, tissue engineering scaffolds, wound healing, and diagnostic platforms. Their versatility makes them attractive for a wide range of biomedical applications (24). The future prospects of mucoadhesive microspheres are promising and diverse. Through ongoing research and technological advancements, they have the potential to revolutionize drug delivery, enable localized therapy, improve vaccination strategies, overcome mucosal barriers, facilitate combination therapies, integrate with nanotechnology, and find applications in various biomedical fields.

2. Conclusion

The primary objective of the mucoadhesive microsphere is to provide controlled release with improved bioavailability and drug delivery to certain body locations. As a model for regulated drug delivery methods, the mucoadhesion process can be applied to a number of medication candidates. Microspheres provide several benefits, including safety and masking, a slower rate of disintegration, and specific targeting of the active ingredient. They can also be individually altered for controlled release. Therefore, this method will also play a significant role in the creation of novel medications using more sophisticated procedures and materials in the future.

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3. References

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