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Mucoadhesive Microspheres: A Concise Review

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Abstract
Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc. which modulates the release and absorption characteristics of the drug. Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesion is the most vital concept that is widely utilized in most of the novel drug delivery systems *via* mucosal membrane of buccal, nasal, digestive tract, etc when administered through oral, nasal or any other route. The mucoadhesive microspheres prepared by different techniques are widely used in sustained delivery of drugs with improved bioavailability and targeting efficacy. Mucoadhesive microspheres exhibit a prolonged residence time at the site of application or absorption and facilitate an intimate contact with the underlying absorption surface and thus contribute to improved and/or better therapeutic performance of drugs. Hence, uptake and consequently bioavailability of the drug is increased and frequency of dosing reduced with the result that patient compliance is improved.
Key words: Microspheres, Mucoadhesion, Mucoadhesive polymers, Bioadhesive polymers, Controlled drug delivery

Introduction

Mucoadhesive drug delivery system are the systems which utilizes the property of bio adhesion of certain polymers which become adhesive on hydration and can be used for targeting a drug to a particular region of the body for extended periods of time. The term mucoadhesion was coined for the adhesion of the polymers with the surface of the mucosal layer. Bio adhesions are a phenomenon in which two materials at least one of which is biological and are held together by means of interfacial forces[1,2]. In biological systems, bio adhesion can be classified into 3 types:
1. Adhesion between two biological phases, for example, platelet aggregation and wound healing
2. Adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and bio film formation on prosthetic devices and inserts
3. Adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel
For drug delivery purposes, the term bio adhesion implies attachment of a drug carrier system to a specified biological location. The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion/mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer. In bio adhesion, the polymer is attached to the biological membrane[3-5].

Advantages:
Mucoadhesive systems have three distinct advantages when compared to conventional dosage forms.
1. Readily localized in the region applied to improve and enhance the bioavailability of drugs. E.g. testosterone & its esters, vasopressin, dopamine, insulin and gentamycin etc.
2. Facilitate intimate contact of the formulation with underlying absorption surface. This allows modification of tissue permeability for absorption of macromolecules. e.g. peptides and proteins.
3. Prolong residence time of the dosage form at the site of application and absorption to permit once or twice a day dosing[6,7].

Mechanism of Mucoadhesion:

A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems. Several theories have been proposed to explain the fundamental mechanism of adhesion[8,9].

Theory of Mucoadhesion:

The phenomena of bioadhesion occur by a complex mechanism. Six theories have been proposed, which will explain the mechanism of bioadhesion. The theories are as follows:

Electronic theory: Involves the formation of an electric double layer at the mucoadhesive interface by the transfer of electrons between the mucoadhesive polymer and the mucin glycoprotein network. For example: Interaction between positively charged polymers chitosan and negatively charged mucosal surface which becomes adhesive on hydration and provides an intimate contact between a dosage form and absorbing tissue.

Wetting 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 such substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive amongst the substrate surfaces[7,10,11].

Adsorption Theory: According to this theory, after an initial contact between two surfaces, the material adheres because of surface force acting between the atoms in two surfaces. Two types of chemical bonds resulting from these forces can be distinguished as primary chemical bonds of covalent nature and Secondary chemical bonds having many different forces of attraction likes electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.

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

Mechanical Theory: Explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion[12,13].

Cohesive Theory: Proposes that the phenomena of bio adhesion are mainly due to the intermolecular interactions amongst like-molecules. Based on the above theories, the process of bio adhesion can be broadly classified into two categories,

1. Chemical: Electronic and adsorption theories
2. Physical: Wetting, diffusion and cohesive theory.

The process of adhesion may be divided into two stages. During the first stage (also Known as contact stage), wetting of mucoadhesive polymer and mucous membrane occurs followed by the consolidation stage, where the physicochemical interactions take place[6,8,14].

Methods of Preparation of Mucoadhesive Microspheres:

Mucoadhesive microspheres can be prepared using any of the following techniques.

Coacervation:

This process consists of mainly three steps carried out under continuous agitation. Formulation of three immiscible chemical phases, deposition of coating, rigidization of the coating. Three immiscible phases include a liquid manufacturing vehicle, a core material phase and a coating material phase. The core material is dispersed in a solution of the polymer, the solvent for the polymer being the liquid manufacturing vehicle phase. Microspheres can be prepared by changing the temperature of the polymer solution, By adding salt, Using a non solvent, and also by the addition of an incompatible polymer to the polymer solution and polymer-polymer interaction[2,4].

Pan coating:

In this process, the coating material is applied as solution or as atomized spray to the desired solid core material in the coating pan. Warm air is passed over the coated materials to remove the coating solvent[5,7].

Air suspension:

This process consists of the dispersing of solid particles of core materials in a supporting air stream and the spray coating of the air suspended particles.

Spray drying:

In spray drying, the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100 μm. Microparticles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions. This process is rapid and this leads to the formation of porous micro particles.

Wet inversion technique:

Chitosan solution in acetic acid was dropped in to an aqueous solution of counter ion sodium tripolyposphate through a nozzle. Microspheres formed were allowed to stand for 1 hr and cross linked with 5% ethylene glycol

diglysidyl ether. Microspheres were then washed and freeze dried. Changing the pH of the coagulation medium could modify the pore structure of CS microspheres[9,15].

Hot melt microencapsulation:

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 μm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5 °C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, e.g. poly anhydrides. Microspheres with diameter of 1-1000 μm can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only disadvantage of this method is moderate temperature to which the drug is exposed.

Solvent removal:

It is a non-aqueous method of microencapsulation, particularly suitable for water labile polymers such as the ploy anhydrides. In this method, drug is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride. This mixture is then suspended in silicone oil containing span 85 and methylene chloride. After pouring the polymer solution into silicone oil, petroleum ether is added and stirred until solvent is extracted into the oil solution. The resulting microspheres can then be dried in vacuum[4,8,17].

Evaluation:

1. **Yield of Microspheres**
   The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres[2,3].
   % Yield = (Actual weight of product /Total weight of excipients and drug) x 100
2. **Particle size determination**
   The particle size can be determined by using an optical microscope under regular polarized light, and mean particle size was calculated by measuring 100 particles with the help of a calibrated coulometer[6,8].
3. **Bulk density**
   Bulk density can be determined by three tap method, after filling the weighed quantity of microspheres in a graduated cylinder, the volume occupied by microspheres should be determined[11,12].
4. **Optical Microscopy**
   This method was used to determine particle size by using optical microscope (Meizer OPTIK) The measurement was done under 450x (10x eye piece and 45x objective) and100 particles were calculated[9,14].
5. **Scanning Electron Microscopy (SEM)**
   Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample slab with the help of double sided sticking tape and coated with gold film under reduced pressure[12,16].
6. **Entrapment Efficiency**
   Microspheres containing of drug should be crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr, and was filtered then assayed by UV-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content[17].
7. **Swelling Index**
   This technique was used for Characterization of sodium alginate microspheres were performed with swelling index technique Different solution (100 mL) were taken such as (distilled water, buffer solution of pH(1.2, 4.5, 7.4) were taken and alginate microspheres (100 mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37˚C and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper[5,9].
8. **In vitro wash-off test:**
   A 1 cm x 1 cm piece of rat stomach mucosa was tied onto a glass slide (3 inch x 1 inch) using a thread. Microsphere was spread onto the wet, rinsed, tissue specimen and the prepared slide was hung onto one of the groves of the USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that that the tissue specimen regular up and down movements in a beaker containing the simulated gastric fluid. At the end of every time interval, the number of microsphere still adhering on to the tissue was counted and there adhesive strength was determined[18].
9. ***In Vitro* drug release:**
   To carry out In Vitro drug release, accurately weighed 50 mg of loaded microspheres were dispersed in dissolution fluid in a beaker and maintained at 37±2 °C under continuous stirring at 100 rpm. At selected time intervals 5 mL samples were withdrawn through a hypodermic syringe fitted with a 0.4 μm Millipore filter and replaced with the same volume of pre-warmed fresh buffer solution to maintain a constant

volume of the receptor compartment. The samples were analyzed spectrophotometrically. The released drug content was determined from the standard calibration curve of given drug[8,9].

10. *In vitro* diffusion studies:

In Vitro diffusion studies were performed using in vitro nasal diffusion cell. The receptor chamber was filled with buffer maintained at 37 ± 2 °C. Accurately weighed microspheres equivalent to 10 mg were spread on sheep nasal mucosa. At selected time intervals 0.5 mL of diffusion samples were withdrawn through a hypodermic syringe and replaced with the same volume of pre warmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples were analyzed spectrophotometrically[19,20].

Conclusion

Novel drug delivery systems achieved a great interest in recent years in the field of modern pharmaceutical formulations. Mucoadhesive microspheres serve as a unique carrier system for many pharmaceuticals that can be tailored to adhere to any mucosal tissue in the body. They can be used not only for sustained release but also for targeted delivery of the drugs to specific sites in the body. Mucoadhesive microspheres have been proved as a promising tool in delivery of drugs to a particular site in controlled or sustained manner, as they deliver the drug to a particular site for longer duration, the absorption of drug increased and hence, the bioavailability of the drug get increased. Therefore, it can be say that in future also mucoadhesive microspheres will play an important role in the development of new pharmaceuticals employing more advanced techniques and materials.

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