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Review Article

MUCOADHESIVE MICROSPHERES: A SHORT REVIEW

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ABSTRACT

Carrier technology provides an interesting as well as an intelligent approach for the delivery of drug. It offers delivery of drug by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc. Microspheres constitute an important part of this particulate drug delivery system because of their small size and other efficient properties. Mucoadhesive microspheres provide better drug absorption as they get adhere to the mucosal surface and release drug for prolonged time. This article reviewed about the mucoadhesive microspheres, their methods of preparation and their evaluation in brief.

Keywords: mucoadhesive microspheres, methods of preparation of mucoadhesive microspheres, evaluation of mucoadhesive microspheres.

INTRODUCTION

Recently the novel dosage forms which can control the release rate and target the active drug molecule to a particular site have attained a great formulation interest. Microspheres are one of the novel drug delivery system which posses several applications and are made up of assorted polymers [1].

Microspheres are small spherical particles (typically 1 µm to 1000 µm), sometimes referred to as microparticles. The microspheres can be made up of either natural or synthetic polymers [2].

Generally microspheres posses' potentiality to be employed for targeted and controlled/extended release of drug, but incorporating mucoadhesive properties to microspheres will furthermore improve absorption and bioavailability of the drugs[3-6]. Mucoadhesive microspheres enhance the intimate contact with the mucus layer, and drug targeting to the absorption site by anchoring bacterial adhesions [7], plant lectins[8], antibodies[9] etc. Tailored mucoadhesive microspheres offers the possibilities of localized as well as controlled release of drugs by adherence to any mucosal tissue present in eye, nasal cavity, urinary, and GI tract.

Advantages of Mucoadhesive Microspheres [2]

1. Provide constant and longer therapeutic effect.
2. Reduces the frequency of daily administration and thereby improve the patient compliance.
3. Improve the absorption of drug hence improve the bioavailability of drug and reduce the chances of adverse effects.
4. The morphology of microspheres permits a controllable variability in degradation and drug release.

Limitation of Mucoadhesive Microspheres [2]

Some of the disadvantages were found to be as follows

1. The release from the formulations may get modified.
2. The release rate may vary from a variety of factors like food and the rate of transit though gut, mucin turnover rate etc.
3. Differences in the release rate can be found from one dose to another.
4. Any loss of integrity in release pattern of the dosage form may lead to potential toxicity.
5. These kinds of dosage forms cannot be crushed or chewed.

Mucoadhesion

Bioadhesion is a phenomenon in which two materials at least one of which is biological in nature are held together by means of interfacial forces. The term "mucoadhesion" define the adhesion of the polymers with the surface of the mucosal layer [10].

Mucus Membranes [11]

Mucus membranes are the moist surfaces lining walls of various body cavities such as the gastrointestinal and respiratory tracts.

Mucus is secreted by the goblet cells. Mucus is present either as a gel layer adherent to the mucosal surface or in suspended form or as a luminal soluble. The major components of all mucus gels are mucin glycoprotein, water, lipids, and inorganic salts. The mucus serves as a protective barrier and for lubrication also.

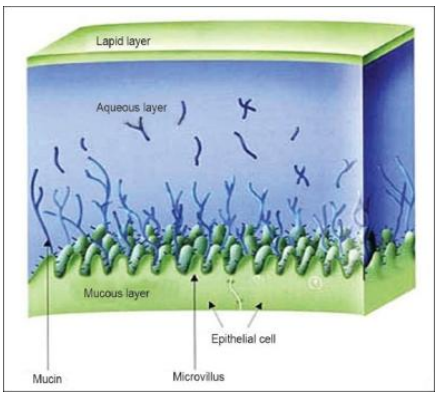

Figure 1: Structure of Mucus Membrane

Mechanism of Mucoadhesion [12]

As stated, mucoadhesion is the attachment of the drug along with a suitable carrier to the mucosal layer. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains.

Mucoadhesion has the following Mechanism

1. Intimate contact between a mucoadhesive delivery system and mucosal membrane (wetting or swelling phenomenon)

2. Penetration of the mucoadhesive delivery system into the tissue or into the surface of the mucous membrane (interpenetration, figure 2 shows the mechanism of mucoadhesion[13] :

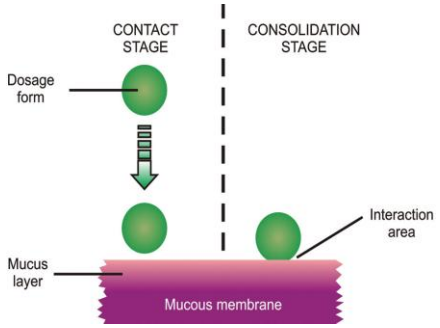

Figure 2: Mechanism of Mucoadhesion

Theories Of Mucoadhesion [14]

Different theories are involved in the mucoadhesion which are as follows

1. The electronic theory
2. The wetting theory
3. The adsorption theory
4. The diffusion theory
5. The mechanical theory, and
6. The cohesive theory

1. The Electronic Theory

According to this theory an electrical double layer is formed on the transfer of the electrons among the mucoadhesive and mucosal membrane**.**

2. The Wetting Theory

This theory is applicable for liquids, postulates that the lower the contact angle of liquid on substrate surface there will be greater affinity for adhesion.

3. The Adsorption Theory

According to this theory the mucoadhesive get adsorbed on the mucosal surface by intermolecular forces, viz. Vander Waal's forces, hydrogen bonding etc.

4. The Diffusion Theory

This theory illustrates the forming of a network structure among the mucoadhesive and the mucosal surface by diffusion of the polymers chains present on the mucoadhesive surface.

5. The Mechanical Theory

Explains the formation of an interlocked structure by the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the mucoadhesive substrate resulting in mucoadhesion.

6. The Cohesive Theory

According to this theory the phenomena of mucoadhesion is mainly due to the intermolecular interactions amongst like-molecules

Factors Affecting Mucoadhesion [14]

The mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors.

Polymer Based Factors Molecular weight of the polymer, concentration of polymer, stereo chemistry of polymer, chain length of polymer, hydration of polymer.

Physical Factors pH at polymer substrate interface, swelling of polymer, applied strength, contact time.

Physiological Factors Mucin turnover rate and diseased state.

Materials Used In the Formulation of Mucoadhesive Microspheres [15]

Mucoadhesive microspheres are made up by using mucoadhesive polymers. Mucoadhesive polymers can be of either natural or synthetic in origin. Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes:

- Polymers that become sticky on placing them in water and achieve their mucoadhesion due to stickiness.
- Polymers that adhere through nonspecific, noncovalent interactions that is primarily electrostatic in nature.
- Polymers that bind to specific receptor site on tile self surface.

CLASSIFICATION OF MUCOADHESIVE POLYMERS

There are various mucoadhesive polymers of synthetic and natural origin, which are classified in Table 1.

Table 1: A short list of mucoadhesive polymers[16].

Synthetic polymers	Natural polymers
Hydroxy propyl methyl cellulose (HPMC)	Chitosan
Poly(acrylic acid) polymers (carbomers, polycarbophil)	Sodium alginate
Poly vinyl pyrrolidone (PVP)	Pectin
Poly vinyl alcohol (PVA)	Locust bean gum
Poly hydroxyethyl methylacrylate	Guar gum
Poly ethylene oxide	Xanthan gum
Sodium carboxy methyl cellulose (Na CMC)	Karaya gum
Hydroxyl ethyl cellulose (HEC)	Gelatin
Hydroxy propyl cellulose (HPC)	Tragacanth
Ethyl cellulose (EC)	Soluble starch
Methyl cellulose (MC)	Lecithin

Methods Of Preparation Of Mucoadhesive Microspheres

Mucoadhesive microspheres can be prepared by using different techniques like:

1. Complex coacervation
2. Hot melt microencapsulation
3. Single emulsion technique
4. Double emulsion method
5. Solvent removal
6. Ionotropic gelation
7. Phase inversion method
8. Spray drying

1. Complex Coacervation[17,18]

Principle of this method is under suitable conditions when solutions of two hydrophilic colloids were mixed, result into a separation of liquid precipitate. In this method the coating material phase, prepared by dissolving immiscible polymer in a suitable vehicle and the core material is dispersed in a solution of the coating polymer under constant stirring. Microencapsulation was achieved by utilizing one of the methods of phase separation, that is, by changing the temperature of the polymer solution; by changing the pH of the medium, by adding a salt or an incompatible polymer or a non-solvent to the polymer solution; by inducing a polymer polymer interaction. Generally coating is hardened by thermal cross linking or desolvation techniques, to form a self sustaining microsphere.

2. Hot Melt Microencapsulation

Microspheres of polyanhydride copolymer of poly bis(p-carboxy phenoxy) propane anhydride with sebacic acid were firstly prepared by this method[19]. In this metod the polymer is firstly melted and then the solid drug particles are added to it with continuous mixing. The prepared mixture is then suspended in a non-miscible solvent like silicone oil with stirring and heated at the temperature above the melting point of the polymer with continuous stirring so as to get stabilized emulsion. The formed emulsion is cooled to solidify polymer particles followed by filtration and washing of the microspheres with petroleum ether.

3. Single Emulsion Technique [12]

The microspheres of natural polymers are prepared by single emulsion technique. The polymers and drug are dissolved or dispersed in aqueous medium followed by dispersion in organic medium e.g. oil, results in formation of globules, and then the dispersed globule are cross linked by either of heat or by using the chemical cross-linkers. The chemical cross-linkers used are formaldehyde, glutaraldehyde, diacid chloride etc.

4. Double Emulsion Method

This method is firstly described by Ogawa Y et al. in year 1988, and is the most widely used method of microencapsulation [20]. In this method an aqueous solution of drug and polymer is added to the organic phase with vigorous stirring to get primary water-in-oil emulsion. This emulsion was then poured to a large volume of water containing an emulsifier like polyvinyl alcohol or

polyvinylpyrrolidone, under stirring, to get the multiple emulsions (w/o/w); and stirring was continued until most of the organic solvent evaporates, leaving solid microspheres. The microspheres are then washed and dried.

5. Solvent Removal

This is a non-aqueous method of microencapsulation and is most suitable for water labile polymers such as the polyanhydrides. The method involves dissolving the polymer into volatile organic solvent and the drug is dispersed or dissolved in it, this solution is then suspended in the silicone oil containing span 85 and methylene chloride under stirring, then petroleum ether is added and stirred until solvent is extracted into the oil solution [21]. The obtained microspheres were then subjected for vacuum drying.

6. Ionotropic Gelation

This method was developed by Lim F and Moss RD [22]. Using this method Microspheres are formed by dissolving the gel-type polymers, such as alginate, in an aqueous solution followed by suspending the active ingredient in the mixture and extruding the solution through needle to produce micro droplets which fall into a hardening solution containing calcium chloride under stirring at low speed. Divalent calcium ions present in the hardening solution crosslink the polymer, forming gelled microspheres.

7. Phase Inversion Method

The method involves addition of drug into dilute polymeric solution, in methylene chloride; and resultant mixture is poured into an unstirred bath of strong non-solvent, petroleum ether, in a ratio of 1: 100. Microspheres produced are then clarified, washed with petroleum ether and air dried [23, 24].

8. Spray Drying

This method involves dissolving/dispersing of the drug into the polymer solution which is then spray dried. By this method the size of microspheres can be controlled by manipulating the rate of spraying, feeding rate of polymer drug solution, nozzle size, and the drying temperature [25-27].

DRUG LOADING IN MICROSPHERE [12]

The drugs are loaded in the microspheres principally using two methods i.e. during the preparation of the microsphere or after the preparation of the microsphere by incubating them with the drug solution.

The active components may be loaded by means of the physical entrapment, chemical linkage and surface absorption. It was found that maximum of drug loading in microspheres may be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables like presence of additives, method of preparation, heat of polymerization, agitation intensity etc.

The loading of drug after the preparation of microspheres may be achieved by incubating them with high concentration of the drug in a suitable solvent. Here drug may be loaded in the microspheres via penetration or diffusion of the drug through the pores present in the microsphere as well as by absorption of drug on the surface of microspheres. The solvent is then removed, leaving drug-loaded microsphere.

DRUG RELEASE KINETICS [12]

Release of drug is an important consideration in case of microspheres. Many theoretically possible mechanisms for the release of drug from the microsphere may be as follows:

- Liberation of the drug due to polymer erosion or degradation.
- Self diffusion of drug through the pore of the microspheres.
- Release of the drug from the surface of the polymer.
- Pulsed delivery initiated by the application of an oscillating or sonic field.

EVALUATION OF MUCOADHESIVE MICROSPHERES

The microspheres are evaluated for the following parameters.

1. Particle Size and Shape

Light microscopy (LM) and scanning electron microscopy (SEM) both can be used to determine the size, shape and outer structure of microspheres [12].

2. Surface Characterization of The Mucoadhesive Microspheres

Data from the scanning electron microscopy, scanning tunneling microscopy and the electron microscopy provides insight to the surface morphology of microspheres and the morphological changes produced through degradation of polymer. Changes in the surface morphology occurring through degradation of polymer can be studied by incubating the microspheres in the phosphate buffer saline at different intervals of time [28]. It was found that microspheres with the coarser surface improve the adhesion through stronger mechanical interactions, while smooth surface of the microspheres leads to weak mucoadhesive properties [4, 29].

3. Surface Charge Study

From photon correlation spectroscopy data the surface charge (zeta potential) of the mucoadhesive microspheres can be determined. The surface charge can be determined by relating measured electrophoretic mobility into zeta potential with in-built software based on the Helmholtz– Smoluchowski equation [30]. Zeta potential is an indicator of particle surface charge, which can be used to predict and control the adhesive strength, stability, and the mechanisms of mucoadhesion. Process of mucoadhesion involves interactions between the mucus and mucoadhesive polymers, and is influenced by their structure including their charge. Measurement of zeta potential of microspheres and mucus helps to predict electrostatic interactions during mucoadhesion[31].

4. Entrapment Efficiency

The entrapment efficiency of the microspheres or the percent entrapment can be determined by keeping the microspheres into the buffer solution and allowing lysing. The lysate obtained is filtered or centrifuged and then subjected for determination of active constituents as per monograph requirement. The percent entrapment efficiency is calculated using following equation [12]:

% Entrapment = Actual content/Theoretical content x 100

5. Swelling Index

Swelling index illustrate the ability of the mucoadhesive microspheres to get swelled at the absorbing surface by absorbing fluids available at the site of absorption ,which is a primary requirement for initiation of mucoadhesion[32]. The percent swelling value can be determined using following equation.

Percent swelling = DT - D0 / D0 × 100

Where, D0 = weight of dried microspheres

DT = weight of swelled microspheres

6. *In- Vitro* Release Study

Standard IP/BP/USP dissolution apparatus is used to study *in-vitro* release profile in the dissolution media that is similar to the fluid present at the absorption site as per monograph, using rotating basket or paddle type dissolution apparatus [33].

7. *Ex-Vivo* Mucoadhesion Study

The mucoadhesive property of the microspheres is evaluated on goat's intestinal mucosa by using phosphate buffer, as per monograph. Weighed microspheres are spread onto wet rinsed tissue specimen and immediately thereafter the slides are hung onto the arm of a USP tablet disintegrating test machine with suitable support at 37^0C. The weight of microspheres leached out at different intervals is measured. The % mucoadhesion is calculated by the following equation [34]:

$$\% \text{ Mucoadhesion} = \frac{Wa - W1}{Wa} \text{ X } 100$$

Where,

Wa is the weight of microspheres applied

W_1 is the weight of microspheres leached out

CONCLUSION

Novel drug delivery systems achieved a great interest in recent years in the field of modern pharmaceutical formulations. 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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