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A REVIEW OF MUCOADHESIVE MICROSPHERES

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ABSTRACT

Microspheres constitute an important part of the novel drug delivery system by virtue of their small size and efficient carrying capacity. Due to their long residence time, bioadhesive characteristics mucoadhesion can be coupled to microspheres to develop mucoadhesive microspheres. Bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are held together for a prolonged time period by means of interfacial forces. Microspheres are the carrier linked drug delivery system in which particle size is ranges from 1 to 1000 µm range in diameter having a core of drug and entirely outer layers of polymer as a coating material. Mucoadhesive microspheres have advantages like efficient absorption and improved bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, controlled and sustained release of drug from dosage form and exact targeting of drugs to the absorption site. The present study aims to provide an overview of various aspects of mucoadhesive microspheres, methodology of preparation of mucoadhesive microspheres, method of evaluation, and their applications in drug delivery.

KEYWORDS: Mucoadhesion, Mucoadhesive microsphere, 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 possess 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 possess 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

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

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

Types of microspheres

Mucoadhesive microspheres, magnetic microspheres, floating microspheres, radioactive microspheres, biodegradable polymeric microspheres, and synthetic polymeric microspheres.

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.

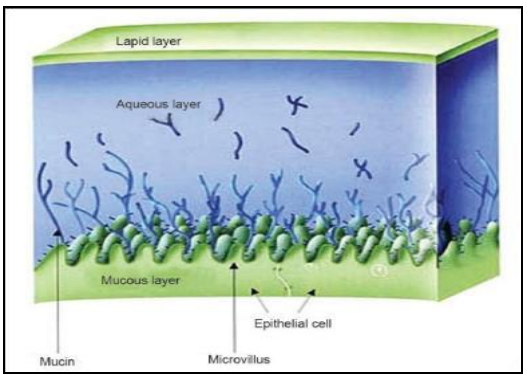

Figure 1: Structure of Mucus Membrane.

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 :

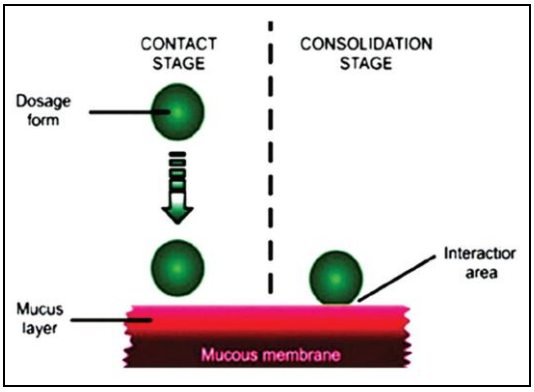

Figure 2: Mechanism of Mucoadhesion.

Characteristics of an Ideal Mucoadhesive Polymer[13]

1. The polymer and its degradation products should be non-toxic and should be non-absorbable from the GI tract
2. It should be non-irritant to the mucus membrane
3. It should adhere quickly to most tissue and should possess some site specificity
4. It should allow easy incorporation of the drug and should offer no hindrance to its release
5. The polymers must not decompose on storage or during the shelf life of the dosage form
6. The cost of the polymer should not be high so that the prepared dosage form remains competitive

MATERIALS USED IN THE FORMULATION OF MUCOADHESIVE MICROSPHERES[14]

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[15]

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

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by microencapsulation technique. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross-linking, drug of cross-linking, evaporation time, co-precipitation, etc. The various methods of preparations are:

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

1. Complex Coacervation[16,17]

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 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.[18] In this method 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

The microspheres of natural polymers are prepared by single emulsion technique.[19] 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. Emulsion cross-linking method

In this method, the drug is dissolved in aqueous gelatin solution which is previously heated for 1 hr at 40°C. The solution is added dropwise to liquid paraffin while stirring the mixture at 1500 rpm for 10 minutes at 35°C, results in w/o emulsion then further stirring is done for 10 minutes at 15°C The produced microspheres are washed respectively 3 times with acetone and isopropyl alcohol which then air dried and dispersed in 5 ml of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross-linking and then 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. Examples for this technique is gelatin microspheres.[21]

6. 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.[22] The obtained microspheres were then subjected for vacuum drying.

7. Ionotropic Gelation

This method was developed by Lim F and Moss RD.[23] 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.

8. 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.[24,25]

9. 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.[26- 28]

DRUG LOADING IN MICROSPHERE

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

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.

2. Surface Characterization of the Mucoadhesive Microspheres

Data from the scanning electron microscopy, scanning tunnelling 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.[29] 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.[4,30]

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.[31] 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.[32]

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[19]:

$$\text{Entrapment efficiency} = \frac{\%\text{Drug loading}}{\%\text{Theoritical loading}} \text{x } 100$$

Where,

$$\%\text{Drug loading} = \frac{\text{Weight of drug in microsphere}}{\text{Weight of microsphere}}$$

5. Percentage yield

Percentage yield will be calculated to know about the efficiency of any method. Thus, it helps in selection of appropriate method of production.[33]

$$\%\text{Yield} = \frac{\text{Total weight of microparticle}}{\text{Total weight of polymer}} \times 100$$

6. 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.[34] The percent swelling value can be determined using following equation (Wg−Wi).

$$\text{Percent swelling} = \frac{Wg - Wi}{Wg} \times 100$$

Where,
Wi - Initial weight of microspheres,
Wg - Final weight of microspheres.

7. *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.[35]

8. *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 370C. The weight of microspheres leached out at different intervals is measured. The % mucoadhesion is calculated by the following equation[36]:

$$\%\text{mucoadhesion} = \frac{Wa - W1}{W1} \times 100$$

Where,
Wa is the weight of microspheres applied
W1 is the weight of microspheres leached out

9. Stability Studies
The microspheres were placed in screw capped glass container and stored at ambient humidity condition, room temperature, (27±2ºC), oven temperature (40±2ºC) and in refrigerator (5-8ºC) for a period of 60 days, and the microspheres were analysed for drug content.[37]

10. Kinetics of drug release
The analysis of the drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of mucoadhesive controlled release systems. As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, Higuchi and the Korsemeyer- Peppas equations. The order of drug release from the mucoadhesive microspheres was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the mucoadhesive controlled release systems was studied by using the Higuchi equation and the Korsemeyer - Peppas equation.

Zero Order Release Kinetics
It defines a linear relationship between the fraction of drug released versus time. $\mathbf{Q = k_0 t}$. Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics
Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is: $\mathbf{\ln (1-Q) = - K_1 t}$. Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant. Thus, a plot of the logarithm of the fraction of drug undissolved against the time will be linear if the release obeys the first order release kinetics.

Higuchi equation
It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time. $\mathbf{Q = K_2 t^{½}}$. Where, K_2 is the release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation.10 This equation describes drug release as a diffusion and erosion process based on the Fick's law, square root time dependant.

Power Law
In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppa's and Korsemeyer equation (Power Law). $\mathbf{M_t/M = K t^n}$. Where, M_t is the amount of drug released at time t and M is the amount released at time , thus the M_t /M is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent. To characterize the mechanism for both the solvent penetration and the drug release, the value of n can be used as abstracted in table 1a. A plot between log of M /M and log of t time will be linear if the release obeys Peppa's and Korsemeyer equation and the slope of this plot represents "n"value.

COMPATIBILITY STUDY
Differential scanning calorimetry (DSC)
It is a thermoanalytical technique in which the amount of heat required to increase the temperature of sample and reference is measured as a function of temperature. DSC thermograms of the microspheres will be recorded with DSC insturument. Accurately weigh samples of the drug are taken in the pans. An empty aluminum pan can be used as a reference pan. The system will be purged with nitrogen gas. Heating will be done at a fix rate.

Fourier transform infrared (FTIR) spectroscopy
IR spectra of the microsphere will be recorded using FTIR spectrophotometer between the ranges by making a pellet of the samples with KBr. The resultant spectra will then compared with a standard reference and observe for any type of deviation from the standard.

APPLICATIONS OF MICROSPHERES

The brief outline of various applications of microsphere is explained as follows.[38]

1. Microspheres in chemotherapy

The most promising application of microspheres are possible to used as carriers for anti- tumor agents. Enhanced endocytic activity and leaky vasculature administrated microspheres. Stealth microspheres are prepared by coating with soluble polyoxy ethylene. The accumulation of non-stealth microspheres in Reticulo Endothelial System (RES) may also be exploited for cancer chemotherapy.[39-41]

2. Microspheres for DNA Delivery

Microspheres have been recently used as a delivery vehicle for the transfer of plasmid DNA which leads to improve the transfer of plasmid DNA and their stability in the bio- environment.[42] Truong-Le & Co workers (1998) developed a novel system for gene delivery based on the use of DNA-gelatin microspheres/ nanoparticles formed by salt induced complex coacervation of gelatin & plasmid DNA**.**

3. Fluorescent microspheres

These are made up of polystyrene or poly vinyl toluene, mono disperse system ranging in size from 20nm to 4µm. Preparation of fluorescent microspheres comprising, swelling the polymeric microsphere so that fluorescent dyes may enter the microsphere pores. Unswelling the polymeric microspheres so that the fluorescent dyes become physically entrapped in the pores.[43]

4. Adjuvant effect for vaccines

An adjuvant effect of the microspheres/nanoparticles with either matrix entrapped or surface adsorbed vaccines have been demonstrated in several studies on substances or oral administration. "Kreuter & Co-workers" observed that Poly methyl methacrylate microspheres containing the influenza antigen induced significant antibody response. Oral delivery of antigens with microspheres may be an elegant means of producing an increase Immunoglobin A (Ig A) antibody response.

5. Microspheres for Ocular delivery

The most applications of drug loaded ophthalmic delivery systems are for glaucoma therapy, especially cholinergic agonists like pilocarpine. The short elimation half life of aqueous eye drops can be extended from a very short time (1-3 min) to prolonged time (15-20 min) using microspheres which have biodegradable properties eg: Poly alkyl cyano acrylate.

6. Microspheres for Lymph targeting

The major purpose of lymph targeting is to provide an effective anticancer chemotherapy to prevent the metastasis of tumor cells by accumulating the drug in the regional lymph node. Example: ü Poly alkyl cyanoacrylate microspheres bearing anticancer drugs for tumor of peritoneal cavity.

ü Poly (lactide-co-glycolide) microspheres for the lymphatic of diagnostic agents.

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 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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