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Review Article

A review: mucoadhesive microsphere.

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ABSTRACT
Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesive microspheres are the carrier linked drug delivery system in which particle size is ranges from 1-1000 μm range in diameter having a core of drug and entirely outer layers of polymer as coating material. 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. In recent years such mucoadhesive microspheres have been developed for oral, buccal, nasal, ocular, rectal and vaginal routes for either systemic or local effects. The objective of this article is review the principles underlying the development and evaluation of mucoadhesive microspheres and the research work carried out on these systems.

KEYWORDS
Mucoadhesive microsphere.

1. INTRODUCTION

1.1. Multiparticulate Drug Delivery System

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Recent trends indicate that single and multiparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping to attain different release patterns as well as reproducible and short gastric residence time [1].

Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microsphere, nanoparticles, etc., which modulates the release and absorption characteristics of the drug. Microspheres / Microparticles constitute an important part of this particulate drug delivery system by virtue of their small size and efficient carrier characteristics. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Such systems often use macromolecules as carriers for the drugs [2].

Micro particulates are small solid particles within the size range of 1-1000μm. Depending upon the method of preparation, the drug is dissolved, entrapped, and encapsulated in the micro particle matrix. Microspheres are systems in which the drug is surrounded by a polymer membrane. Microparticles gives easy administration way to deliver macromolecules by various routes and effectively control the release of drugs over the periods ranging from few hours to months, because of effective protection of encapsulated drug against degradation. It is an important part of a novel drug delivery system as it prepares for prolonged or controlled drug delivery and to improve the bioavailability of the drug and also to target the specific sites in the body [3].

1.2. Mucoadhesive Microspheres

The oral route of drug administration is the most largely used and preferred means of drug delivery to the systemic circulation of the body.

However the drugs which are administered through oral route in the form of conventional dosage have limitations of their inability to limit and localize the system at gastrointestinal tract. Microencapsulation is one of the approaches to enhance the oral bioavailability. Due to their small size and efficient carrier characteristics, microspheres constitute an important part of particulate novel drug delivery system. The achievement of microspheres is limited due to their short residence time at the site of absorption and it can be subdued by for providing an intimate contact of the drug delivery system with the absorbing membrane. This can be accomplished by coupling bioadhesion characteristics to microspheres and developing mucoadhesive microspheres. [5]

1.3. Advantages of Mucoadhesive Microspheres [6]

- Reduces the frequency of administration and thereby improve the patient compliance.
- The use of specific bioadhesive molecules allows for possible targeting of particular sites or tissues, for example the gastrointestinal (GI) tract.

- As a result of adhesion and intimate contact, the formulation stays longer at the delivery site, improving API bioavailability using lower API concentrations for disease treatment.
- Offers an excellent route, for the systemic delivery of drugs with high first-pass metabolism, thereby offering a greater bioavailability.
- Uniform and wide distribution of drug throughout the gastrointestinal tract, which improves the drug absorption.
- Prolonged and sustained release of drug and maintenance of the therapeutic plasma drug concentration.
- Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of the intestine can be administered by this route. E.g. buccal, sublingual, vagina etc.

1.4. Disadvantages of mucoadhesive microspheres [6]

- The release rate may vary from a variety of factors like food and the rate of transit though gut, mucin turnover rate etc.
- Any loss of integrity in the release pattern of the dosage form may lead to potential toxicity.
- Differences in the release rate can be found from one dose to another.

1.5. Method of Preparation of Mucoadhesive Microspheres [7, 8]

1.5.1. Orifice ionic gelation technique

In this method sodium alginate and mucoadhesive polymer is dissolved in purified water to form a homogeneous polymer solution. The active metabolite is added to the polymer solution and mixed thoroughly with stirrer to form viscous dispersion. The resulting dispersion is added manually drop wise into calcium chloride (10%) solution through a syringe no.18. The added droplets are retained in the calcium chloride solution for 15 minutes to complete the curing reaction and to produce spherical rigid microspheres. The microcapsules will be collected by decantation and product thus separated washed repeatedly with water and dried at 45^0c for 12 hours.

1.5.2. Solvent evaporation

It is the most extensively used method of microencapsulation. Buffered or plain aqueous solution of the drug (may contain viscosity building or stabilizing agent) is added to an organic phase consisting of the polymer solution in solvents like dichloromethane (or ethyl acetate or chloroform) with vigorous stirring to form the primary water in oil emulsion. This emulsion is then added to a large volume of water containing an emulsifier like PVA or PVP to form the multiple emulsions (w/o/w). The double emulsion, so formed is then subjected to stirring until most of the organic solvent evaporates, leaving solid microspheres. The microspheres can then be washed, centrifuged and lyophilize to obtain the free flowing and dried microspheres.

1.5.3. Hot melt microencapsulation

In this method, the polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50μm. The mixture is suspended in a non-miscible solvent (like silicon oil), continuously stirred, and heated to 50^o 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. Polyanhydrides. Microspheres with a diameter of 1-1000μm 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.

1.5.4. Solvent removal

It is a non-aqueous method of microencapsulation particularly suitable for water labile polymers such as the Polyanhydrides. In this method, drug is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like ethylene 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 the solvent is extracted into the oil solution. The resulting microspheres can then be dried in a vacuum.

1.5.5. Hydrogel microspheres

Microspheres made of gel type polymers, such as alginates, are produced by dissolving the polymer in an aqueous solution, suspending the active ingredient in the mixture and extruding through a precision device, producing micro droplets which fall into a hardening bath that is slowly stirred. The hardening bath usually contains calcium chloride solution, whereby the divalent calcium ions cross linking the polymer formed gelled microspheres. The method involves an all aqueous system, which eliminates residual solvents in microspheres.

1.5.6. Spray drying

In this process, the drug may be dissolved or dispersed in the polymer solution and spray dried. The quality of spray dried microspheres can be improved by the addition of plasticizers, e.g. citric acid, which promote polymer coalescence on the drug particles and hence promote the formation of spherical and smooth surfaced microspheres. The size of microspheres can be controlled by the rate of spraying, the feed rate of polymer drug solution, nozzle size, and the drying temperature.

1.5.7. Phase inversion microencapsulation

The process involves the addition of drug in a dilute solution of the polymer (usually 1-5%, w/v in methylene chloride). The mixture is poured into an unstirred bath of strong non solvent (petroleum ether) in a solvent ratio of 1:100, resulting in the spontaneous production of microspheres in the size range of 0.5-5.0μm can then be filtered, washed with petroleum ether and dried with air. This simple and fast process of microencapsulation involves relatively little loss of polymer and drug.

1.6. Materials Used In the Preparation of Microsphere[9]

Microspheres used usually are polymers. Polymers have played a significant role in designing such systems so as to enhance the residence time of the active agent at the desired location. Polymers used in the mucosal delivery system may be of natural or synthetic origin. In this section we will briefly discuss some of the common types of mucoadhesive polymers.

1.6.1. Synthetic polymers

Poly (acrylic acid) polymers (Carbomer, Polycarbophil), Cellulose derivatives (MC, EC, HPMC, Sodium CMC), Poly (Hydroxyethyl methylacrylate), Poly (ethylene oxide), Poly (vinyl pyrrolidone), Poly (vinyl alcohol).

1.6.2. Natural polymers

Guar gum, Xanthan gum, Lectin, Soluble starch, Tragacanth, Sodium alginate, Karaya gum, Gelatin, Pectin, Chitosan

1.7. Characteristics of an Ideal Mucoadhesive Polymer **[10]**

1. The polymer and its degradation products should be nontoxic and should be absorbed from the GI tract.
2. It should be non irritant to the mucus membrane.
3. It should preferably form a strong covalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to most tissues and should possess some site specificity.
5. It should allow easy incorporation of the drug and should offer no hindrance to its release.
6. The polymers must not decompose on storage or during the shelf life of the dosage form.
7. The cost of the polymer should not be high so that the prepared dosage form remains competitive.

1.8. Theories of Mucoadhesion [18, 19]

1.8.1. Electronic theory

According to this theory, electron transfer occur upon contact of adhesive polymer with a mucus glycoprotein network because of differences in their electronic structures. This results in the formation of electrical double layer at the interface. E.g .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.

1.8.2. Absorption 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, including electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.

1.8.3. Diffusion theory

According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permeable 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 turns depends on the value of the molecular weight between cross linking and decreases significantly as the cross linking density increases.

1.8.4. Wetting theory

The wetting theory postulates 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 substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive among the substrate surface.

1.8.5. Cohesive theory

The cohesive theory proposes that the phenomena of bioadhesion are mainly due to intermolecular interaction amongst like molecule. Based upon the above theories, the process of bioadhesion can broadly be classified into two categories namely chemical (electron and absorption theory) and physical (wetting, diffusion and cohesive theory).

1.8.6. Fracture theory

This is perhaps the most-used theory in studies on the mechanical measurement of mucoadhesion. It analyses the force required to separate two surfaces after the adhesion is established. This force, Sm, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, Fm, and the total surface area, A_0 Since the fracture theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains, involved in the adhesive interaction (eq.1):

Sm= Fm/Ao ……. (1)

1.8.7. Mechanical theory

Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface of a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions, thereby aiding dissipating energy and can be considered the most important phenomenon of the process.

1.9. Characterization of Microspheres

1.9.1. Drug content estimation [31]

Drug loaded microsphere (100 mg) were powdered and suspended in 100 ml 0.1N HCl solution and kept for 24hr. It was stirred for 5 minutes and filtered by whatmann filter paper. Drug content in the filtrate was determined using spectrophotometer at 280 nm.

% Drug content = Actual drug content / total wt. of microsphere taken× 100.

1.9.2. Drug entrapment efficiency [32]

Microspheres equivalent to 5 mg of Drug were crushed using a glass mortar and pestle and the powdered microspheres were suspended in 25 ml of 0.1N HCl. After 24 hrs, the solution was filtered, 1 ml of the filtrate was pipette out and diluted to 10 ml and analyzed for the drug content by using UV Visible Spectrophotometer at 280 nm.

The drug entrapment efficiency was calculated using the following formula.

Entrapment efficiency = (Actual drug content/theoretical drug content) ×100.

1.9.3. Mucoadhesive Test [33, 34]

The mucoadhesive property of microspheres was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised pieces of goat intestinal mucosa were mounted onto glass slides with cotton thread. About 20 microspheres were spread on to each prepared glass slide and immediately thereafter the slides were hanged to USP II tablet

disintegration test. When the test apparatus was operated, the sample was subjected to slow up and down movement in the test fluid at 37 ^{0}C contained in a 1-liter vessel of the apparatus. At an interval of 1hours up to 8 hours the machine was stopped and number of microspheres still adhering to mucosal surface was counted. The test was performed in 0.1 N HCl. The adhesion number was determined by the following equation:

$Na=N/N_0\times100$

Where Na is adhesion number, N_0 is total number of particles in a particular area, and N is number of particles attached to the mucosa after washing.

1.9.4. Particle Size Analysis [33]

The sample of prepared microspheres was randomly selected and their size was determined using an electronic microscope with the help of eye piece and stage micro meter. In all measurements at least 50 beads in five different fields were examined. Each experiment was carried out in triplicate.

1.9.5. In vitro drug release study [35]

The in vitro release of drug from mucoadhesive microspheres was measured using basket type dissolution test apparatus. Drug microsphere equivalent to 50 mg were placed in the basket. The volume of dissolution medium was 900 ml and maintained at 37±0.5^{0}C at 100 rpm. An aliquot of 5ml of the solution was withdrawn at predetermined time intervals and replaced by 5ml of fresh dissolution medium immediately. The samples were assayed via UV-Vis spectrophotometer (lab India) at 280 nm after filtration through a 0.45µm membrane filter. The dissolution medium was used as a reference while UV scanning of the samples. All dissolution tests were performed in triplicate.

1.9.6. Fourier transforms infrared spectroscopy [36, 28]

Fourier transform infrared spectra were obtained using Shimadzu FTIR-8400S spectrometer, Japan. Samples of drug, physical mixtures and optimized formulation of microsphere were taken for the study. The scanning range was 500 to 4000 cm^{-1}and the resolution was 4 cm^{-1}.

1.9.7. Powder X-ray diffraction (PXRD) [36, 37]

PXRD patterns were recorded using BRUCKER D2 PHASER A26-X1 ABOB2A, fitted with a copper target, a voltage of 40 kV, and a current of 30mA. The scanning rate was 1°/min over a 2 θ range of 1-50°. PXRD patterns were traced for drug, physical mixture and formulation. The samples were slightly ground and packed into the aluminum sample container.

1.9.8. Differential scanning calorimetric (DSC) **[36, 37]**

DSC analysis of the samples was carried out on a Perkin-Elmer DSC7, USA. Samples (6.5-10 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10 °C/min over the temperature range of 5 and 300 °C. DSC analysis was carried out under nitrogen gas flow of 20 lb/in^2.

1.9.10. Scanning Electron Microscopy and Morphology Characterization (SEM) **[30]**

The surface morphology and internal texture of the microspheres were studied by scanning electron microscopy. Scanning Electron Microscope JSM 6330 JEOL (Japan). Acceleration voltage set at 3Kv at Magnification level 65x, 500x, 2000x, 5000 x. The samples were then randomly scanned and microphotographs were taken on different magnification. Then morphological characteristics of microspheres were determined from photograph of SEM.

1.10. Application of Microspheres in Pharmaceutical Industry

1. Ophthalmic Drug Delivery

Microspheres developed using polymer exhibits favorable biological behavior such as bioadhesion, permeability enhancing properties, and interesting physicochemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles.

Eg. Chitosan, Alginate, Gelatin.

2. Oral drug delivery

The ability of microspheres containing polymer to form films permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make microspheres more suitable for oral drug delivery applications. Eg. Chitosan, Gelatin.

3. Gene delivery

Microspheres could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. Eg. Chitosan, Gelatin, viral vectors, cationic liposomes, polycation complexes.

4. Nasal drug delivery

Polymer based drug delivery systems, such as microspheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Eg. Starch, Dextran, Albumin, Chitosan+ Gelatin.

5. Intratumoral and local drug delivery

In order to deliver paclitaxel at the tumor site in therapeutically relevant concentration, polymer films are fabricated. Mixture of drug has promising potential for use in controlled delivery in the oral cavity. Eg. Gelatin, PLGA, Chitosan and PCL.

6. Buccal drug delivery

Polymer is an excellent polymer to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. Chitosan, Sodium alginate.

7. Gastrointestinal drug delivery

Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug . eg. Eudragit, Ethyl cellulose+Carbopol BSA, Gelatin.

8. Transdermal drug delivery

Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Eg. Chitosan, Alginate, PLGA.

9. Colonic drug delivery

Polymer has been used for the specific delivery of insulin to the colon. Eg. Chitosan.

10. Vaginal drug delivery

Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer is widely used for the treatment of mycotic infections of the genitourinary tract.

Eg. Chitosan, Gelatin, PLGA.

11. Targeting by using microparticulate carriers

Pellets are prepared with polymer by using the extrusion/spheronization technology.

Eg. Chitosan, Microcrystalline cellulose.

2. CONCLUSION

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 gets increased. These carrier systems will also increase the residence time of the drug in the gastrointestinal tract. Mucoadhesive drug delivery is a promising area for systemic delivery of orally inefficient drugs as well as an attractive alternative for noninvasive delivery of potent peptide and perhaps protein drug molecules. Therefore, it can be said 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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