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Mucoadhesive Microspheres – A Review

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A B S T R A C T

The current article focuses on the principles of mucoadhesive drug delivery systems based on adhesion to biological surfaces. Microspheres constitute a major part of novel drug delivery system because of their small size and other efficient properties. Mucoadheisve microspheres exhibit a prolonged residence time at the site of application or absorption and facilitate an intimate contact with the biological surface and thus contribute to improve and better therapeutic performance of drugs. This paper discussed briefly about the mucoadhesive microspheres, mechanism of mucoadhesion, current status of various methods of preparation *i.e.* Ionic Gelatin, Simple Emulsification Phase Separation, Emulsion Solvent Evaporation, Co-acervation and Phase Separation, Spray Drying, Hot Melt Microencapsulation, Hydroxyl Appetite Microspheres in Sphere Morphology, Preparation of microspheres by Tripolyphosphate etc. and methods of evaluations *i.e.* Size, Shape and surface characterization, Swelling index, Encapsulation efficiency, *In-vitro* wash-off test, *In-vitro* dissolution studies. Mucoadhesive drug delivery systems is one of the most important novel drug delivery systems with its various advantages and it has a lot of potential in formulating dosage forms for various chronic diseases.

Keywords: Mucoadhesive Microspheres, Mucoadhesion

A R T I C L E I N F O

CONTENTS

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1. Introduction

Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had 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 microspheres, nanoparticles, liposomes, *etc.* which modulates the release and absorption characteristics of the drug. Microspheres constitute an important part of these particulate DDS by virtue of their small size and efficient carrier characteristics. However, the success of these novel DDS is limited dueto their short residence time at the site of absorption. Itwould, therefore, be advantageous to have means for providingan intimate contact of the DDS with absorbing membranes.It can be achieved by coupling mucoadhesion characteristics to microspheres and developing novel delivery systems referred to as "mucoadhesive microspheres."Microspheres are defined as spherical particles having size less than 2000μm and made up of polymer matrix in which therapeutic substance is dispersed throughout the matrix at the molecular or macroscopic level. The rationale of developing mucoadhesive microsphere drug delivery system lies behind the fact that the formulation will be 'held' on a biological surface for localized drug delivery. The API will be released close to the site of action with a consequent enhancement of bioavailability. [1]

The oral route of drug administration is the most commodious and preferred means of drug delivery to systemic circulation of 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 gastro-intestinal tract. Microencapsulation is one of the approaches to enhance the oral bioavailability. Due to their small size andefficient carrier characteristics, microspheres constitute an important part of particulate novel drug deliverysystem. The successes of microspheres are limited due to their short residence time at the site of absorption and itcan 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". [2]

Mucoadhesive microspheres include micro particles of 1-2000μm range in diameter which comprises of entiremucoadhesive polymer or having an outer coating of it. Bioavailability of the drugs are enhanced due to their highsurface to volume ratio which provides an intimate contact with the mucus layer, resulting in controlled andsustained release of drug from dosage form and specific targeting of drugs to the absorption site. [3] Despite the limited loading capacity of drug, bioadhesive micro/nano particles have been widely investigated for three major features: [4]

1. Immobilization of particles on the mucosal surface by adhesion after modification of surface properties via bioadhesive polymers.
2. Very large specific surface between the dosage forms and the oral mucosa.
3. Sustained release of entrapped drug, leading to higher absorption.

2. Advantages of Mucoadhesive Microspheres

As a result of adhesion and intimate contact, the formulation stays longer at the delivery site and thus improves API bioavailability. It can be allowed the disease treatment at lower API concentrations for. It offers an excellent route for the systemic delivery of drugs with high first-pass metabolism, there by offering a greater bioavailability. The use of specific bioadhesive molecules allows possible targeting of drug molecules at particular sites or tissues, for example the gastrointestinal (GI) tract. It Increase residence time of formulation at target site and control API release which may lead to lower administration frequency. Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site. So, it will improve patient compliance and convenience due to less frequent drug administration. It cause Uniform and wide distribution of drug throughout the gastrointestinal tract which improves the drug absorption. It provides Prolonged and sustainedrelease of drug. It maintains therapeutic plasma drug concentration. Reduction in fluctuation insteady state levels produce better control of disease condition and reduced intensity of localor systemic side effects. The process ability is better (improving solubility, dispersibility, flow ability). It increase safety margin of high potency drugs due to better control of plasma levels. Drugs which are unstable in the acidic environment or destroyed by enzymatic oralkaline environment of intestine can be administered by this route e.g. buccal, sublingual, vagina. [5, 6]

Advantages of mucoadhesive microspheres drug delivery systems [7]

1. 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.
2. The use of specific bioadhesive molecules allows for possible targeting of particular sites or tissues, for example the gastrointestinal (GI) tract.
3. Increased residence time combined with controlled API release may lead to lower administration frequency.
4. Offers an excellent route, for the systemic delivery of drugs with high first-pass metabolism, there by offering a greater bioavailability.
5. Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.
6. Better patient compliance and convenience due to less frequent drug administration.
7. Uniform and wide distribution of drug throughout the gastrointestinal tract which improves the drug absorption.
8. Prolonged and sustained release of drug.

9. Maintenance of therapeutic plasma drug concentration.
10. Better processability (improving solubility, dispersibility, flow ability).
11. Increased safety margin of high potency drugs due to better control of plasma levels.
12. Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.

3. Mechanism of Mucoadhesion

Mucoadhesion or 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. For drug delivery purpose, the term "bioadhesion" implies attachment of a drug carrier system to a specific 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 mucous coat, the phenomenon is referred to as "Mucoadhesion". Mucoadhesion has been widely promoted as a way of achieving site-specific drug delivery through the incorporation of mucoadhesive hydrophilic polymers within pharmaceutical formulations such as "microspheres" along with the active pharmaceutical ingredient **[7]**.

The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and hence increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must dominate. Each step can be facilitated by the nature of the dosage form and how it is administered. Thus, the mechanism of mucoadhesion is generally divided in two steps:

1. The contact stage
2. The consolidation stage

The first stage or the contact stage **(Figure: 1)** is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In the consolidation step **(Figure: 1)**, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticize the system, allowing the mucoadhesive molecules to break free and to link up by weak van-der Waals and hydrogen bonds.

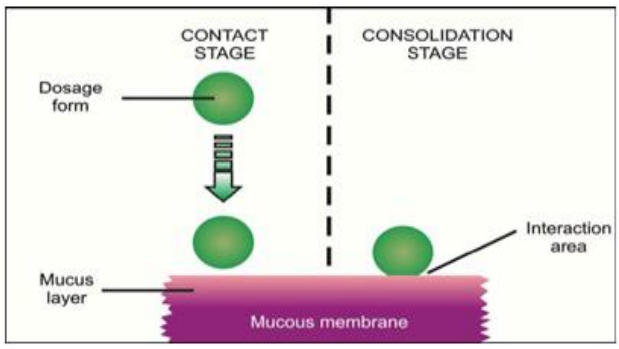

Figure 1: Two stages of mucoadhesion

Themucoadhesive/Mucosa Interaction [19]

Chemical bonds: For adhesion to occur, molecules must bond across the interface. These bonds can arise in the following way:

a. Ionic bonds-where two oppositely charged ions attract each other via electrostatic interactions to form a strong bond (e.g., in a salt crystal).
b. Covalent bonds- electrons are mutually shared, in pairs, between the bonded atoms in order to 'fill' the orbital in both. These are also strong bonds.
c. Hydrogen bonds- where a hydrogen atom, when covalently bonded to electronegative atoms such as oxygen, fluorine or nitrogen, carries a slight positively charge and is therefore is attracted to other electronegative atoms. The hydrogen can therefore be thought of as being shared, and the bond formed is generally weaker than ionic or covalent bonds.
d. Van-der Waals bonds-these are some of the weakest forms of interaction that arise from dipole- dipole and dipole-induced dipole attractions in polar molecules, and dispersion forces with non-polar substances.
e. Hydrophobic bonds-more accurately described as the hydrophobic effect, these are indirect bonds (such groups only appear to be attracted to each other) that occur when non-polar groups are present in an aqueous solution. Water molecules adjacent to non-polar groups form hydrogen bonded structures, which lowers the system entropy. There is therefore an increase in the tendency of non-polar groups to associate with each other to minimize this effect.

4. Methods of Preparation

Mucoadhesive microspheres can be prepared by using different techniques like: [8]

Ionic gelatin method [9]

This method was developed by Lim F and Moss RD[(10)]. It involves reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer were dispersed in purified water (25 mL) to form a homogeneous polymer mixture. The active pharmaceutical ingredient was added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a lab-scale developed spray device with an air compressor into calcium chloride (10 % w/v) solution. The addition was done with continuous stirring; the added droplets were retained in the calcium chloride solution for 15 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried.

Double Emulsion Method [11]

This method is firstly described by Ogawa Y *et al.* in year 1988, and is the most widely used method of

microencapsulation[12]**.** 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.

Spray drying [13]

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 1-100µm.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.

Hot Melt Microencapsulation [14, 15]

In this method was first used by Mathiowitz and Langerto prepare microsphere of polyanhydride copolymer of poly[bis (*p*-carboxyphenoxy) propane anhydride]with sebacic acid the polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50m. 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.* polyanhydrides. Microspheres with 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.

Simple Emulsification Phase Separation Technique [9]

A 2.5 % (w/v) chitosan solution in aqueous acetic acid was prepared. This dispersed phase was added to continuous phase (125 mL) consisting of light liquid paraffin and heavy liquid paraffin in the ratio of 1:1 containing 0.5 % (w/v) Span 85 to form a water in oil (w / o) emulsion. Stirring was continued at 2000 rpm using a 3- blade propeller stirrer. A drop-by-drop solution of a measured quantity (2.5 mL each) of aqueous glutaraldehyde (25 % v/v) was added at 15, 30, 45, and 60 minutes. Stirring was continued for 2.5 hours and separated by filtration under vacuum and washed, first with petroleum ether (60 °C - 80 °C) and then with distilled water to remove the adhered liquid paraffin and glutaraldehyde, respectively. The microspheres were then finally dried in vacuum desiccators.

Solvent removal method [16, 17]

It is a non-aqueous method of microencapsulation, also suitable for water labile polymers such as the polyanhydrides. Carino and co-workers used this method for preparing microspheres. In this method, drug was dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride. This mixture was then suspended in silicone oil containing Span 85 and methylene chloride. After pouring the polymer solution into silicone oil, petroleum ether was added and stirred until solvent was extracted into the oil solution. The resulting microspheres were then dried under vacuum.

Hydrogel Microspheres [18]

Microspheres made of gel-type polymers, such as alginate, are produced by dissolving thepolymer 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 crosslink the polymer forming gelled microspheres. The method involves an "all-aqueous" system and avoids residual solvents in microspheres. Lim and Moss[10] developed this method for encapsulation of live cells, as it does not involve harsh conditions, which could kill the cells. The surface of these microspheres can be further modified by coating them with polycationic polymers, like polylysine after fabrication. The particle size of microspheres can be controlled by usingvarious size extruders or by varying the polymer solution flow rates

Phase separation coacervation technique [6]

This process is based on the principle of decreasingthe solubility of the polymer in organic phase toaffect the formation of polymer rich phase called thecoacervates. In this method, the drug particles aredispersed in a solution of the polymer and anincompatible polymer is added to the system whichmakes first polymer to phase separate and engulf thedrug particles. Addition of non-solvent results in thesolidification of polymer. Polylactic acid (PLA) microspheres have been prepared by this method byusing butadiene as incompatible polymer. Theprocess variables are very important since the rate ofachieving the coacervates determines the distributionof the polymer film, the particle size andagglomeration of the formed particles. Theagglomeration must be avoided by stirring thesuspension using a suitable speed stirrer since as theprocess of microspheres formation begins the formedpolymerize globules start to stick and form theagglomerates. Therefore the process variables arecritical as they control the kinetic of the formedparticles since there is no defined state of equilibrium attainment.

Hydroxyl appetite (HAP) microspheres in sphere morphology [9]

This was used to prepare microspheres with peculiar spheres in sphere morphology. Microspheres were prepared by o/w emulsion followed by solvent evaporation. At first o/w emulsion was prepared by dispersing the organic phase (Diclofenac sodium containing 5 % w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules. This prevented the droplets from co-solvencing and helped them to stay individual droplets, while stirring the DCM

was slowly evaporated and the droplets solidify individually to become microspheres.

Preparation of microspheres by Tripolyphosphate [20]

Chitosan solution of 2.5 % w/v concentration was prepared. Microspheres were formed by dropping the bubble-free dispersion of chitosan through a disposable syringe (10 mL) onto a gently agitated (magnetic stirrer) 5 % or 10 % w/v TPP solution. Chitosan microspheres were separated after 2 hrs by filtration and rinsed with distilled water, and then they were air dried.

Evaluation of Mucoadhesive Microspheres:

Evaluation of mucoadhesive microspheres can be done by the following parameters:

Particle size, Shape and Morphology [20,21,22,23]

All the microspheres were evaluated with respect to their size and shape using optical microscope fitted with an ocular micrometer and a stage micrometer. The particle diameters of more than 100 microspheres were measured randomly by optical microscope. Scanning Electron photomicrographs of drug-loaded microspheres were taken. Asmall amount of microspheres was spread on gold stub. Afterwards, the stub containing the sample wasplaced in the Scanning electron microscopy (SEM). A Scanning electron photomicrograph was taken atan acceleration voltage of 20KV.

Angle of contact [2, 24]

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. Contact angle is measured at 20º within a minute of deposition of microspheres.

Bulk Density/ Tapped Density [6]

The microspheres fabricated are weighed and transferred to a 10-ml glass graduated cylinder. The cylinder is tapped using an autotapped density apparatus until the microsphere bed volume is stabilized. The density is estimated by the ratio of microsphere weight to the final volume of the microspherebed.

Entrapment Efficiency [11,25]

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

$$Entrapment\ Efficiency = \frac{Actual\ Drug\ Content}{Theoretical\ Drug\ Content} \times 100$$

Swelling index [6,26]

This technique is used for Characterization of sodium alginate microspheres. Different solution (100mL)are taken such as (distilled water, buffer solution ofpH (1.2, 4.5, 7.4) are taken and alginate microspheres(100mg) are placed in a wire basket and kept on theabove solution and swelling is allowed at 37 0C andchanges in weight variation between initial weight ofmicrospheres and weight due to swelling is measuredby taking weight periodically and soaking with filter paper.The swelling index of the microsphere is calculatedby using the formula:-

$$S.I. = \frac{We - Wo}{Wo}$$

Where,

Wo= Initial weight of the dry microspheres,

We = Weight of the swollen microspheres at equilibrium swelling in the media.

***In-vitro* drug release [27]**

The release rate of drug from mucoadhesive microspheres was determined usingdissolution testing apparatus 2 (paddle type).The dissolution test was performed using900 mL of suitable dissolution medium at37± 0.50 C and 50 rpm. A sample (10 mL) of the solution was withdrawn from thedissolution apparatus hourly for 24 hrs, andthe sample were replaced with freshdissolution medium to maintain the sickcondition. The samples were filtered througha membrane filter and diluted to a suitableconcentration with same dissolutionmedium. Absorbance of these solutions wasmeasured at suitable λ_{max} using a doublebeam spectrophotometer. Cumulative percentage drug release was calculated usingan equation obtained from a standard curveand same studies were performed in 6.8 pHphosphate buffer solutions.

***Ex-Vivo* Mucoadhesion Study [11,28]**

The mucoadhesive property of the microspheres is evaluated on goat's intestinal mucosa by using phosphate buffer, as per monograph. Weighed microspheresare spread onto wet rinsed tissue specimen and immediately thereafter the slides are hung onto the arm of a USP tablet disintegrating test machine with suitablesupport at 370C. The weight of microspheres leached out at different intervals is measured. The % mucoadhesion is calculated by the following equation:

$$\%\ Mucoadhesion = \frac{No.of\ microspheres\ adhered}{No.of\ microspheres\ applied} \times 100$$

***In vitro* diffusion studies [13, 29]**

In Vitro diffusion studies were performed using in vitro nasal diffusion cell68. 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.

5. Applications of Mucoadhesive Microspheres

The potential use of microspheres in the pharmaceutical industry has been considered since the 1960s for the following applications [30]:

- Taste and odour masking

- Conversion of oils and other liquids to solids for ease of handling
- Protection of drugs against the environment (moisture, light, heat, and/or oxidation) and vice-versa (prevention of pain on injection)
- Delay of volatilization
- Separation of incompatible materials (other drugs or excipients such as buffers)
- Improvement of flow of powders
- Safe handling of toxic substances
- Aid in dispersion of water-insoluble substances in aqueous media
- Production of sustained-release, controlled-release, and targeted medications
- Reduced dose dumping potential compared to large implantable

Medical applications [9]

- Release of proteins, hormones and peptides over extended period of time.
- Gene therapy with DNA plasmids and also delivery of insulin.
- Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intraarterial/ intravenous application.
- Tumour targeting with doxorubicin and also treatments of leishmaniasis.
- Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
- Used in isolation of antibodies, cell separation and toxin extraction by affinity Chromatography.
- Used for various diagnostic tests for infectious diseases like bacterial, viral and fungal.

Radioactive microsphere's application [9]

- Can be used for radioembolisation of liver and spleen tumours.
- Used for radiosynvectomy of arthiritis joint, local radiotherapy, interactivity treatement.
- Imaging of liver, spleen, bone marrow, lung etc., and even imaging of thrombus in deep vein.
- Thrombosis can be done.

Other applications [9]

- Fluorescent microspheres can be used for membrane based technologies for flow cytomettry, cell biology, microbiology, Fluorescent Linked Immuno-Sorbent Assay.

Yttrium-90 can be used for primary treatment of hepatocellular carcinoma and also used for pretransplant management of HCC with promising results.

6. Conclusion

Control release of drug profile has been a major aim of pharmaceutical research. Microsphere drug delivery system provides opportunities for designing new controlled and delayed released formulations. Mucoadhesive microspheres offer unique carrier system for many pharmaceuticals and can be tailored to adhere to any mucosal tissue, including those found in eyes, oral cavity and throughout the respiratory, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs. Dosing frequency and loss of drug also reduced by use of such type of formulations. Variety of opportunities offered by microspheres like protection and masking, reduction in dissolution rate, spatial targeting of the active ingredient. Mucoadhesive microspheres drug delivery system have been gaining a lot of interest of various researchers and scholars with the aim of achieving controlled release with enhanced bioavailability over longer periods of time, and for drug targeting to various sites in the body.

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