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Mucoadhesive Microsphere as a Drug Delivery System: A Review

Shahina N.S*, R Deepa Manohar
Department of Pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, Neyyattinkara-695124, TVM, Kerala, India

Abstract

Transporting system of drug delivery in the body is an interesting as well as an wondered approach . It deliver the drug by combining the drug to a vector particle such as microspheres, mucoadhesive microspheres, nanoparticles, liposomes etc. Microsphere offers an important part of technology of drug delivery system by the specialty of their tiny size and capable carrier capacity. Because of their short retaining time , bioadhesive characteristics can be compained to microspheres to develop mucoadhesive microspheres. Bioadhesion is 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 force. Mucoadhesive microspheres have high residence time at the site of application and their by enhance the bioavailability of the drug due to high surface volume ratio, prolonged and preside delivery of drug from dosage form.

Key words: Microsphere, Mucoadhesion, Residence time, Bioavailability

INTRODUCTION

The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation of body. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of microsphere constitute an important part of particulate drug delivery systems by virtue of their small size and efficient carrier capacity[1]. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period, enhancement of activity of shorter half-life drugs, elimination of side effects, reducing frequency of dosing and wastage of drugs, optimized therapy and better patient compliances.

Drug action can be improved by developing new drug delivery system, such as the mucoadhesive microsphere drug delivery system. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to a bioavailability increase and both local and systemic effects . The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation of body. However oral administration of most of the drugs in conventional dosage forms has short-term limitations due to their inability to restrain and localize the system at gastro-intestinal tract. 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 outer layers of polymer as coating material. The success of these microspheres is limited due to their long residence time at site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane. This can be achieved by coupling bioadhesion characteristics to microspheres and developing "mucoadhesive microspheres". Mucoadhesive microspheres have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.

MICROSPHERES

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). Microspheres are sometimes referred to as microparticles . However, the success of these microspheres is limited due to their short residence time at site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane. Microspheres can encapsulate many types of drugs including small molecules, proteins, and nucleic acids and are easily administered through a syringe needle. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time.

APPROACHES TO FABRICATE GASTRO-RETENSIVE SYSTEMS

- Floating or Low density delivery systems
- Swelling systems
- High density systems
- Bioadhesive or mucoadhesive systems

MUCOADHESIVE MICROSPHERE

Mucoadhesive microspheres include microparticles and microcapsules of 1 to 1000 µ*m* in diameter consisting either entirely of mucoadhesive polymer or having an outer coating with adhesive property .Microspheres have the potential to be used for controlled as well as spatial drug delivery. Incorporating mucoadhesivenes to microspheres leads to efficient absorption and enhanced

bioavailability of drug. Specific targeting of drug to the absorption site is achieved by using homing devices (ligand) like plant lactin, bacterial adhesion etc on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to mucosal linings of GIT, thus offering the possibilities of localized as well as systemic absorption of drug in controlled manner[2].

ADVANTAGES OF MUCOADHESIVE MICROSPHERES

- Prolonged and sustained release of drug.
- Maintenance of therapeutic plasma drug concentration.
- Increased residence time combined with controlled API release may lead to lower administration frequency.
- As a result of adhesion and intimate contact , the formulation stays longer at the delivery site improving API bioavailability.
- The significant cost reduction may be achieved and dose related side effect may be reduced.
- Better patient compliance and convenience due to less frequent drug administration.

The successful development of oral controlled drug delivery systems achieved by using mucoadhesive microspheres, for getting successful gastro intestinal retention and prolonged action mucoadhesive system is very successful approach.

MECHANISM OF MUCOADHESION

Chemical approaches

The process involved in the formation of bioadhesive bonds has been described in three steps, and shown in Figure 1.

a) Wetting and swelling of polymer to permit intimate contact with biological tissue.

b) Interpenetration of bioadhesive polymer chain and entanglement of polymer and mucin chains.

c) Formation of weak chemical bonds between entangled chain.

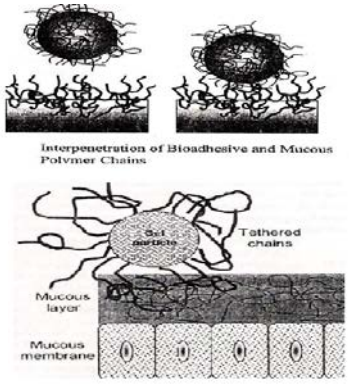

Figure (i).Mechanism of mucoadhesion

THEORIES OF MUCOADHESION[3]:

- ***Electronic theory:***
  Involves the formation of an electric double layer at the mucoadhesive interface by the transfer of electrons between the mucoadhesive polymer and the mucin glycoprotein network
- ***Wetting theory:***
  States that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two such substrate surface are brought in contact with each other in the presence of liquid, the liquid may act as an adhesive amongst the substrate surface.
- ***Absorption theory:***
  According to this theory , after an initial contact between two surfaces, the material adheres because 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 wall forces, hydrogen and hydrophobic bonds.
- ***Diffusion theory:***
  According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact.

FACTORS AFFECTING MUCOADHESION[4]

A) Polymer related factors

Environment related factors affecting mucoadhesion

(i) pH

pH was found to have a significant effect on mucoadhesion. pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different charge density depending on the pH because of the difference in the dissociation of the functional groups on the carbohydrate moiety and amino acids of the polypeptide backbone.

(ii) Applied strength

To place a solid bioadhesive system, it is necessary to apply a defined strength. The adhesion strength increases with the applied strength or with the duration of its application, up to an optimum level.

(iii) Initial contact time

The initial contact time between the mucoadhesives and the mucus layer determines the extent of swelling and the interpenetration of the polymer chains. The mucoadhesive strength increases as the initial contact time increases.

Physico chemical factors

(i) Composition and characteristic of mucous

a) Mucins are synthesized by the goblet cells and special exocrine glands

b) Mucin is of glycoprotein family, having mol.wt.1-40 Dalton

c) Mucin network is negative because of ,

- Presence of sialic acid which has pKa of 2.6
- Presence of charged groups.

(ii) Mucin turn over

The natural turn over of the mucin molecules from the mucus layer is important for at least two reasons, (a) The mucin turn over is expected to limit the residence time of

mucoadhesive dosage form on the mucus layer. (b) Mucin turn over results in substantial amount of soluble mucin molecules. These mucin molecules interact with mucoadhesive before they have a chance to interact with the mucus layer.

(iii) Disease states

The physiological properties of the mucus are known to change during disease conditions such as the common cold, gastric ulcers etc. The exact structural changes taking place in mucus under these conditions are not yet clearly understood.

(iv) Physiological consideration

Membranes of intestinal tracts of the body are covered with a thick gel like structure known as mucin ,which is synthesized by goblet cells and special exocrine glands with mucous cell acini.This bioadhesive mucin consists of highly hydrated, cross-linked, linear, flexible and random coil glycoprotein molecules with net negative charge.

POLYMERS USED IN FORMULATING MUCOADHESIVE DRUG DELIVERY SYSTEM[5]

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

Hydrophilic polymers

The polymers within this category are soluble in water. Matrices developed with these polymers swell when put into an aqueous media with subsequent dissolution of the matrix. The polyelectrolytes extend greater mucoadhesive property when compared with neutral polymers. Anionic polyelectrolytes, e.g. poly (acrylic acid) and carboxymethyl cellulose have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer. Chitosan provides an excellent example of cationic polyelectrolyte, which has been extensively used for developing mucoadhesive polymer due to its good biocompatibility and biodegradable properties.

Hydrogels

Hydrogels can be defined as three-dimensionally crosslinked polymer chains which have the ability to hold water within its porous structure. The water holding capacity of the hydrogels is mainly due to the presence of hydrophilic functional groups like hydroxyl, amino and carboxyl groups. Hydrogels prepared by the condensation reaction of poly (acrylic acid) and sucrose indicated an increase in the mucoadhesive property.

Thiolated polymers

The presence of free thiol groups in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin which can substantially improve the mucoadhesive properties of the polymers e.g. poly (acrylic acid) and chitosan). Various thiolated polymers include chitosan– iminothiolane, poly (acrylic acid)–cysteine, poly (acrylic acid)–homocysteine, chitosan–thioglycolic acid, chitosan–thioethylamidine, alginate–cysteine, poly (methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine.

Lectin-based polymers

Lectins are proteins which have ability to reversibly bind with specific sugar carbohydrate residues and are found in both animal and plant kingdom. The specific affinity of lectins towards sugar or carbohydrate residues provides them with specific cyto-adhesive property and is being explored to develop targeted delivery systems. Lectins extracted from legumes have been widely explored for targeted delivery systems.

METHODS OF PREPARATION

Emulsion cross linking method:

First the drug was dissolved in aqueous gelatin solution which is previously heated for 1 hr at 40°C. The solution is added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 °C, results in w/o emulsion then further stirring is done for 10 min at 15 °C. The produced microspheres are washed respectively three times with acetone and isopropyl alcohol which is then air dried and dispersed in 5ml of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then treated with 100ml of glyciene solution containing 0.1%w/v of tween 80 at 37°C for 10 min. Examples for this technique is Gelatin A microspheres.

Solvent Evaporation:

This is carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent from the polymer of the core material , then polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The core materials may be either water soluble or water insoluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous[6].

Single Emulsion Technique

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[7].

Spray Drying

In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, Acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This

dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100µm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying, shown in Figure 2. 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.

Ionic gelation

In this method drug is added to aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it is added drop wise to a solution containing Ca^{2+}/Al^{3+}. Microspheres which are formed were kept in original solution for 24 hr for internal gellification followed by filtration for separation. The complete release is obtained at pH 6.4-7.4 but the drug will not release in acidic pH. There are two methods by which microspheres can be generated using ionotropic gelation technique that is external ionotropic gelation/cross-linking method and internal ionotropic gelation/emulsification method and it is shown in figure 3[8].

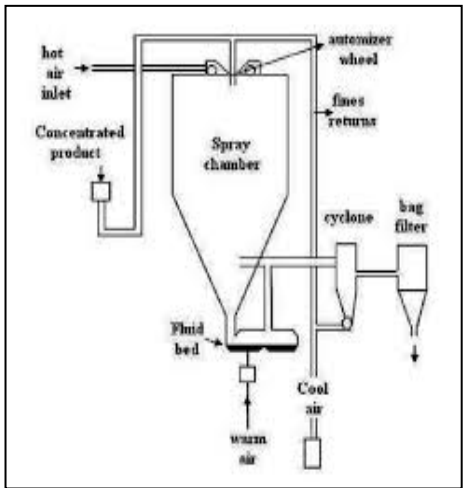

Figure (ii): Spray drying technique

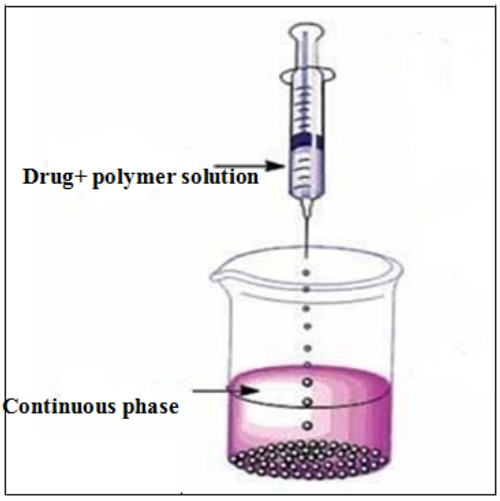

Figure (iii).External ionotropic gelation method

APPLICATIONS OF MUCOADHESIVE MICROSPHERES[9]:

1. Oral drug delivery: The ability of microspheres containing polymer to form films permit its use in the formulaton of film dosage form, as an alternative to pharmaceutical tablets.
2. Gene delivery : Microspheres could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract eg: chitosan ,gelatin etc.
3. Nasal drug delivery: polymer based drug delivery systems, such as microspheres demonstrated to have good bio adhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drug
4. Buccal drug delivery: polymer is an excellent to be used for buccal delivery because it has muco or bio adhesive properties and can act as an absorption enhancer.
5.. Mucoadhesive microspheres are used as targeted drug delivery system for various diseases.
    1. Hypertension
    2. Diabetes mellitus
    3. Peptic ulcer
    4. AIDS

CHARACTERIZATION/ EVALUATION OF MUCOADHESIVE MICROSPHERE

Particle size, Shape and Morphology:

All the microspheres are evaluate 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. A small amount of microspheres was spread on gold stub. Afterwards, the stub containing the sample was placed in the Scanning electron microscopy (SEM)[9].

UV-FTIR (Fourier transform infra red):

The drug polymer interaction and also degradation of drug while processing for microencapsulation can be determined by FTIR. In this method the pellets of drug and potassium bromide are prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra are scanned in the wave number range of 400- 600 cm^{-1}. FTIR study is carried on pure drug, physical mixture, formulations and empty microspheres.

Production Yield:

The production yield of microspheres of various batches using the weight of final product after drying with respect to initial total weight of the drug and polymer used for preparation of mucoadhesive microspheres and percent production yields are calculated as per the formula mentioned below.

Production Yield

$$= \frac{\text{Actual weight of microspheres}}{\text{Total weight of exipients and drug}} \times 100$$

Entrapment Efficiency:

The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph

requirement. The percent encapsulation efficiency is calculated using following equation,

$$\% \text{ Entrapment} = \frac{\text{Actual drug content}}{\text{Theoretical content}} \times 100$$

Swelling Index:

Swelling index was determined by measuring the extent of swelling of microspheres . To ensure the complete equilibrium, exactly weighed amount of microspheres were allowed to swell in given buffer. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using microbalance. The hydrogel microspheres then dried in an oven at 60° for 5 hour until there was no change in the dried mass of sample. The swelling index of the microsphere was calculated by using the formula,

Swelling index= (mass of swollen microspheres - mass of dry microspheres/mass of dried microspheres) ×100[3].

***Ex vivo* Mucoadhesion Study:**

The mucoadhesive property of the microspheres studied using *ex-vivo* mucoadhesion method. In this method, freshly excised piece of goat intestinal mucosa (2 × 3 cm) is mounted onto glass slides with elastic bands. About 100 microspheres were spread onto the wet rinsed intestinal mucosa and there after the support was hung onto the arm of a USP tablet disintegrating test machine. The disintegration machine containing tissue specimen was adjusted for a slow and regular up and down moment in a test fluid at 37˚C taken in a beaker. At the end of 1 h and later at hourly intervals up to 8 h, the machine was stopped and the number of microspheres still adhering onto the tissue was counted and the percentage of mucoadhesion was calculated. The test was performed in pH 1.2 HCl buffer and pH 7.4 phosphate buffer.

***In vitro* drug release:**

To carry out *In Vitro* drug release, accurately weighed 50 mg of loaded microspheres were dispersed in dissolution fluid in a beaker and maintained at 37± 2° C under continuous stirring at 100 rpm. At selected time intervals 5 ml samples were withdrawn through a hypodermic syringe fitted with a 0.4 μm Millipore filter and replaced with the same volume of pre-warmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples were analyzed spectrophotometrically. The released drug content was determined from the standard calibration curve of given drug.

CONCLUSION

The phenomenon of mucoadhesion can be used as model for the controlled drug delivery approaches for a number of drug candidates. Variety of opportunities offered by microspheres like protection and masking, reduction in dissolution rate, special targeting of the active ingredient. The promising aim of mucoadhesive microsphere is to achieving controlled release with enhanced bioavailability and drug targeting to specific sites in the body.

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