



MUCOADHESIVE MICROPARTICULATE DRUG DELIVERY SYSTEM

S.K.Tilloo, T.M.Rasala*, V.V.Kale

Gurunanak College of pharmacy, Nagpur, India.

*Corresponding author's E-mail: tirupati_rasala@yahoo.co.in

Accepted on: 23-03-2011; Finalized on: 01-07-2011.

ABSTRACT

Mucoadhesion is topic of current interest in the design of drug delivery system. Mucoadhesion can be defined as the process by which a natural or a synthetic polymer can adhere to a biological substrate. Mucoadhesive microparticle exhibit a prolonged residence time at the site of application and facilitate an intimate contact with the underlying absorption surface and thus contribute to improved or better therapeutic performance of drug. The current review provides a good insight on mucoadhesive polymers, the phenomenon of mucoadhesion, the various techniques to prepare microparticles and their characterisation.

Keywords: Mucoadhesion, Mucoadhesive polymers, Drug delivery.

INTRODUCTION

The term 'mucoadhesive' is commonly used for materials that bind to the mucin layer of a biological membrane. Mucoadhesion can be defined as a phenomenon of interfacial molecular attractive forces amongst the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time. The substrate possessing bioadhesive property can help in devising a delivery system capable of delivering a bioactive agent for a prolonged period of time at a specific delivery site.

Mucoadhesive polymers have been utilised in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosa. These dosage forms include tablets, patches, tapes, films, semisolids and powders. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups, suitable surface property for wetting mucus/mucosal tissue surfaces and sufficient flexibility to penetrate the mucus network or tissue crevices^{1,2}.

MUCOADHESION MECHANISM

A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems. Several theories have been proposed to explain the fundamental mechanism of adhesion³⁻⁵. A General Mechanism of Mucoadhesion Drug Delivery system is show in Figure 1.

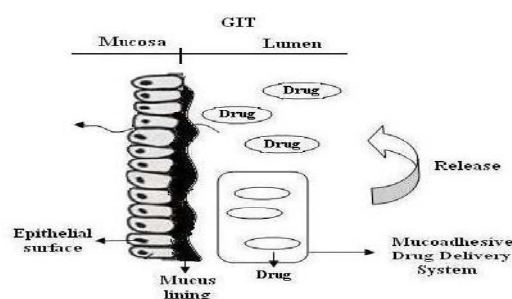


Figure 1: Mechanism of Mucoadhesion

MUCOADHESION THEORIES

The phenomena of bioadhesion occurs by a complex mechanism. Till date, six theories have been proposed which can improve our understanding for the phenomena of adhesion and can also be extended to explain the mechanism of bioadhesion. The theories include: (a) the electronic theory, (b) the wetting theory, (c) the adsorption theory, (d) the diffusion theory, (e) the mechanical theory and (f) the cohesive theory⁶⁻⁹.

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 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 such substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive amongst the substrate surfaces.

Adsorption Theory proposes the presence of intermolecular forces, viz. hydrogen bonding and Vander Waal's forces, for the adhesive interaction amongst the substrate surfaces.

Diffusion Theory assumes the diffusion of the polymer chains, present on the substrate surfaces, across the

adhesive interface thereby forming a networked structure.

Mechanical Theory explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion.

Cohesive Theory proposes that the phenomena of bioadhesion are mainly due to the intermolecular interactions amongst like-molecules.

Based on the above theories, the process of bioadhesion can be broadly classified into two categories.

- 1) **Chemical:** ex. Electronic and adsorption theories
- 2) **Physical:** ex. Wetting, diffusion and cohesive theory methods.

The process of adhesion may be divided into two stages. During the first stage (also known as contact stage), wetting of mucoadhesive polymer and mucous membrane occurs followed by the consolidation stage, where the physico-chemical interactions prevail.

POLYMERS IN MUCOSAL DRUG DELIVERY

Mucoadhesive delivery systems are being explored for the localization of the active agents to a particular location/ site. Polymers have played an important role in designing such systems so as to increase the residence time of the active agent at the desired location. Polymers used in mucosal delivery system may be of natural or synthetic origin¹⁰⁻¹⁴.

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 polyelectrolyte's: 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.

Cationic Polyelectrolyte: Chitosan provides an excellent example of it which has been extensively used for developing mucoadhesive polymer due to its good biocompatibility and biodegradable properties. Chitosan undergoes electrostatic interactions with the negatively charged mucin chains thereby exhibiting mucoadhesive property. The delivery system was prone to dissolution as the time progressed due to the release of the incorporated drug.

Non-ionic Polymers: e.g. poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, poly (vinyl alcohol) and poly (vinyl pyrrolidone), have also been used for mucoadhesive properties. The hydrophilic polymers form

viscous solutions when dissolved in water and hence may also be used as viscosity modifying/enhancing agents in the development of various delivery systems so as to increase the bioavailability of the active agents.

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.

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) in addition to the paracellular uptake of the bioactive agents. 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 the ability to reversibly bind with specific sugar / carbohydrate residues and are found in both animal and plant kingdom in addition to various microorganisms. 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. The various lectins which have shown specific binding to the mucosa include lectins extracted from *Ulex europaeus* I, soybean, peanut and *Lens culinaris*.

Table 1: List of Natural and Synthetic polymers

Synthetic polymers	Natural polymers
Cellulose derivatives	Tragacanth
Polycarbophil	sodium alginate
Poly (ethylene oxide)	Karaya gum
Poly (vinyl pyrrolidone)	Guar gum
Poly (vinyl alcohol).	Gelatin
Poly (hydroxyethyl methylacrylate)	Chitosan
Hydroxyl propyl cellulose	Soluble starch

VARIOUS TECHNIQUES TO PREPARE MICROPARTICLE¹⁵⁻¹⁶

Preparation of Microparticles by Thermal Cross-Linking

Citric acid, as a cross-linking agent was added to 30 mL of an aqueous acetic acid solution of chitosan (2.5% wt/vol) maintaining a constant molar ratio between chitosan and citric acid (6.90×10^{-3} mol chitosan: 1 mol citric acid). The chitosan cross-linker solution was cooled to 0°C and



then added to 25 mL of corn oil previously maintained at 0°C, with stirring for 2 minutes. This emulsion was then added to 175 mL of corn oil maintained at 120°C, and cross-linking was performed in a glass beaker under vigorous stirring (1000 rpm) for 40 minutes. The microspheres obtained were filtered and then washed with diethyl ether, dried, and sieved.

Preparation By Glutaraldehyde Crosslinking

A 2.5% (wt/vol) 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% (wt/vol) Span 85 to form a water in oil (w/o) emulsion. Stirring was continued at 2000 rpm using a 3- blade propeller stirrer (Remi Equipments, Mumbai, India). A drop-by-drop solution of a measured quantity (2.5 mL each) of aqueous glutaraldehyde (25% vol/vol) 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.

Preparation by Tripolyphosphate

Chitosan solution of 2.5% wt/vol 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% wt/vol TPP solution. Chitosan microspheres were separated after 2 hours by filtration and rinsed with distilled water, and then they were air dried.

Emulsification and Ionotropic Gelation Technique

Dispersed phase consisting of 40 mL of 2% vol/vol aqueous acetic acid containing 2.5% wt/vol chitosan was added to the continuous phase consisting of hexane (250 mL) and Span 85 (0.5% wt/vol) to form a w/o emulsion. After 20 minutes of mechanical stirring, 15 mL of 1N sodium hydroxide solution was added at the rate of 5 mL per min at 15-minute intervals. Stirring speed of 2200 rpm was continued for 2.5 hours. The microspheres were separated by filtration and subsequently washed with petroleum ether, followed by distilled water and then air dried.

Preparation of Ethylcellulose Microparticles

A solution of Ethylcellulose in acetone was added to liquid paraffin containing emulgent (Span 85) while stirring at a speed of 1500 rpm. The emulsion was stirred for 5 to 6 hours at 25°C to 30°C. Subsequently, a suitable amount of petroleum ether was added to the dispersion, filtered, and dried at ambient temperature. The resultant microspheres were washed with water followed by petroleum ether to remove traces of liquid paraffin. The microspheres were desiccated under vacuum.

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. 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.

Solvent Evaporation

The processes are 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 for the polymer of the core material is disperse in the polymer solution, 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 in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous. The comparison of mucoadhesive microspheres of hyaluronic acid, Chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelating prepared by complex coacervation were made.

Wet Inversion Technique

Chitosan solution in acetic acid was dropped in to an aqueous solution of counter ion sodium tripolyphosphate through a nozzle. Microspheres formed were allowed to stand for 1 hr and cross linked with 5% ethylene glycol diglycidyl ether. Microspheres were then washed and freeze dried. Changing the pH of the coagulation medium could modify the pore structure of CS microspheres.

Complex Coacervation

CS microparticles can also prepare by complex coacervation, Sodium alginate, sodium CMC and sodium polyacrylic acid can be used for complex coacervation with CS to form microspheres. These microparticles are formed by interionic interaction between oppositely charged polymers solutions and KCl & CaCl₂ solutions. The obtained capsules were hardened in the counter ion solution before washing and drying.



Hot Melt Microencapsulation

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 µm. 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 1-1000 µm 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.

CHARACTERIZATION OF MICROPARTICLES¹⁷⁻¹⁹

Particle Size and Shape

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 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). A Scanning electron photomicrograph was taken at an acceleration voltage of 20KV.

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.

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

Swelling Index

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. 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 h 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 =

$$\frac{\text{mass of swollen microspheres} - \text{mass of dry microspheres}}{\text{Mass of dried microspheres}} \times 100$$

In Vitro Wash-Off Test

A 1 cm x 1 cm piece of rat stomach mucosa was tied onto a glass slide (3 inch x 1 inch) using a thread. Microsphere was spread onto the wet, rinsed, tissue specimen and the prepared slide was hung onto one of the grooves of the USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that that the tissue specimen regular up and down movements in a beaker containing the simulated gastric fluid. At the end of every time interval, the number of microsphere still adhering on to the tissue was counted and there adhesive strength was determined using the formula.

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° 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.

In-Vitro Diffusion Studies

In-Vitro diffusion studies were performed using in vitro diffusion cell. The receptor chamber was filled with buffer maintained at 37±2°C. Accurately weighed microspheres equivalent to 10 mg were spread on sheep mucosa. At selected time intervals 0.5 ml of diffusion samples were withdrawn through a hypodermic syringe and replaced with the same volume of prewarmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples were analyzed spectrophotometrically.

STABILITY STUDIES OF MICROSPHERE

The preparation was divided into 3 sets and was stored at 4°C (refrigerator), room temperature and 40°C (thermostatic oven). After 15, 30 and 60 days drug content of all the formulation was determined spectrophotometrically.

DRUG POLYMER INTERACTION STUDIES

FTIR studies

IR spectroscopy can be performed by Fourier transformed infrared spectrophotometer. The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000- 600 cm⁻¹. FTIR study was carried on pure drug, physical mixture, formulations and empty microspheres.



DSC studies

All dynamic DSC studies can be carried out on drug, physical mixture and formulations. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10°C/min.

CONCLUSION

Recently scientists are trying to improve the bioavailability of active agents by tailoring the properties of the delivery systems instead of designing new active agents. Mucoadhesive polymers may provide an important tool to improve the bioavailability of the active agent by improving the residence time at the delivery site. Mucoadhesive microparticle can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.

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