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MUCOADHESIVE MICROSPHERES

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ABSTRACT
Bioadhesion can be defined as the process by which a natural or synthetic polymer can adhere to a biological substrate. When the biological substrate is a mucosal layer then it is known as mucoadhesion. Mucoadhesion is a currently used in the design of drug delivery system. Mucoadhesive microspheres provide a prolonged residence time at the site of application or absorption and facilitate an intimate contact with the underlying absorption surface and improve or better to therapeutic performance of drug. Mucoadhesive polymer are used to improving drug delivery by promoting the residence time and contact time of the dosage form with the mucous membranes, it adhere the mucosal surface in the body and the drug absorption by mucosal cells may be enhanced or released at the site for an extended period of time and enhanced bio availability of the drug to high surface to volume ratio. In recent years such mucoadhesive microspheres have been developed for oral, buccal , nasal, ocular, rectal, vaginal routes for either systemic or local effects. The aim of this article is review the principles underlaying the mucoadhesive polymer, methods of preparation and evaluation of muco adhesive microspheres.
KEYWORDS: mucosa, mucoadhesion, muco adhesive polymer microspheres

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INTRODUCTION

A primary object of using mucoadhesive formulations orally would achieve a substantial increase in the length of stay of the drug in GI tract Stability problem in the intestinal fluids can be overcome. Therapeutic effect of drugs insoluble in the intestinal fluids can be improved[1].
Mucoadhesive microsphere carrier systems are made from the biodegradable polymers in sustained drug delivery. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems[2,3]. Microspheres form an important part of such novel drug delivery systems. They have varied applications and are prepared using assorted polymers[5].
However, the success of these microspheres is limited owing to their short residence time at the 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[6-9]. This can be achieved by coupling bio adhesion characteristics to microspheres and developing bio adhesive microspheres. Bio adhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing 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[10-13].
To overcome the relativity short GI time and improve localization for oral controlled or sustained release drug delivery systems. The polymers which adhere to the mucin epithelial surface are effective and lead to significant improvement in oral drug delivery based on this three broad categories.
Polymer that becomes sticky when placed in water and owes their bio adhesion to sickness.
Polymers that adhere through non- specific, non-covalent interaction are primarily electrostatic in nature.
Polymer that binds to specific receptor site on the cell valerate[1,5].
Microspheres of biodegradable and non biodegradable polymers have been investigated for sustained release. An important requirement of polymers is that degradation products should be non toxic because such products eventually enter systemic circulation or result in tissue deposition[1,5] .

Mechanism of drug release theoretically the release of drug from biodegrable microspheres classified but in actual practice the mechanism is more complex and an interplay of different mechanisms may operate

I. Degradation controlled monolithic systems.
II. Diffusion controlled monolithic systems.
III. Diffusion controlled reservoir systems.
IV. Erodible poly agent system.

The bio adhesive polymers can be broadly classified in to two groups, namely specific and non specific[14]. The specific bioadhesive polymers e.g. Lectins, Fibrin have the ability to adhere to specific channel structure with in the biological molecules. While the non specific polymers e.g. polyacrylic acid, cyanoacrylate have the ability to bind with both the cell surface and the mucosal layer. Various other polymers, sodium alginate, sodium CMC, guargum, hydroxyl ethyl cellulose, karya gum, methylcellulose, polyethylene glycol, tragacanth, Polyacrylic acid, HPC[15].

Microspheres are spherical, partical size less than 200µm, free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature, solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix having the potential for controlled release of drug[16].

MATERIALS USED

Biodegradable and non biodegradable have been used for the preparation of microspheres, these materials include the polymers of natural and synthetic origin and also modified natural substances, synthetic polymers employed as carrier materials are methyl acrylate, acrolein, lactide, glycolide and their copolymers , ethylene vinyl acetate copolymer, polyanhydrides, the natural polymers are albumin, gelatin, collagen, starch, agarose, carrageenam, chitosan[17-19].

Theories of mucoadhesion

The phenomenon of bioadhesion occurs by a complex mechanism. Till date, six theories have been proposed which can improve our understanding for the phenomenon of adhesion and can also be extended to explain the mechanism of bioadhesion. The theories include (a)The electronic theory proposes transfer of electrons amongst the surface resulting in the formation of an electrical double layer thereby giving attractive forces. (b) 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. (c)The adsorption theory proposes the presence of intermolecular forces, viz. hydrogen bonding and Vanderwaal's forces, for the adhesive interaction amongst the substrate surfaces. (d) The diffusion theory assumes the diffusion of the polymer chains, present on the substrate surfaces, across the adhesive interface thereby forming a networked structure. (e) The mechanical theory explains the diffusion of the liquid adhesives in to the micro cracks and irregularities present on the substrate surface there by forming an interlocked structure which gives rise to adhesion. (f) The cohesive theory proposes that the phenomena of bio adhesion are mainly due to the intermolecular interactions amongst like molecules[20,21].

Based on the above theories, of bio adhesion can be broadly classified in to two types, namely chemical (electronic and adsorption theories) and physical (wetting, diffusion and cohesive theory) methods[22-25].

Bioadhesion may take place either by physical or by chemical interactions. These interactions can be further classified as hydrogen bonds, Vanderwaals force and hydrophobic bonds which are considered as physical interaction while the formation of ionic and covalent bonds[26].

The term "mucoadhesion" is adhesion of the polymers with the surface of the mucosal layer. The mucosal layer is made up of mucus which is secreted by the goblet cells columnar and is a visco elastic fluid. The main components constituting the mucosa include >95% water and > 99% mucin, the other components include protein, lipids and mucopolysaccharides. The gel like structure of the mucus can be attributed to the intermolecular entanglements of the mucin glycoproteins along with the non covalent interactions[21] which results in the formation of a hydrated gel like structure.

Method of preparation of microspheres

The microsphere can be prepared by using several technique section, but the choice of the technique mainly depends on the nature of the polymer used, the drug, the intended use and the duration of therapy. Moreover, the method of preparation and its choice are equivocally determined by some formulation and technology related factors as mentioned below:

1) The particle size.
2) The drug or the protein should not be adversely affected by processes.
3) Reproducibility of the release profile and the method.
4) No stability problem.
5) No toxic product associated with the final product.

Synthetic polymers are now also choice for the control release as well as targeted microparticulate carriers. Different types of methods are employed for the preparation of microsphere.

These include

Single emulsion technique
Double emulsion technique
Polymerization technique

Normal polymerization
Interfacial polymerization
Phase separation coacervation technique
Spray drying and spray congealing
Solvent extraction [27, 28, 29]

Loading of drugs

The drugs are loaded over the microspheres principally using two methods[1] during the preparation of microsphere[2] after the formation of microsphere by incubating them with the drug /protein .the active component can be loaded by means of physical entrapment, chemical linkage and surface adsorption. The entrapment largely depends on method of preparation and nature of the drug and polymer. Maximum loading can be achieved by incorporating the drug during the time of preparation but percent incorporation in preformed microsphere is relatively less but the major advantage of the loading method being their no effect of process variable. the loading is carried out in preformed microsphere by incubating them with high concentration of the drug in a suitable solvent .the drug in these microsphere is loaded via penetration or diffusion of the drug through the pores in the microsphere as well as adsorption on their surface. The solvent is then removed, leaving drug loaded microsphere. The adsorption of the drug/protein depends on the nature of the polymers.

EVALUATION OF MUCOADHESIVE

Properties

Various *in vitro* and *in vivo* methods are used for testing the efficacy of muccoadhesive nature of a polymer matrix commonly used *in vitro* / *in vivo* method include tensile strength measurement, shear strength measurement and cheap based systems whereas various imaging techniques are used for the evaluation of delivery system under *in vitro* conditions.

In vitro tensile strength measurement is done by dipping the filtered by paper in 8% mucin dispersion thereafter, the mucin coated filter paper is placed in a coated with the hydrated polymeric samples for a definite period of time, followed by the determination of the maximum force required to detach the filter paper and polymer surfaces after the mucoadhesive bonding[30] similarly ex vivo experimentation are also done with the exception that the mucin coated filter-paper is replaced with excised mucosal tissues[31-33]. The mucoadhesive properties can also be determined by incubating the hydrated polymer matrix surface kept in contact with the viscoelastic 30% (w/w) mucin solution in water with the subsequent determination of the maximum detachment force required to separate the polymer matrix and mucin solution surfaces after the adhesion. Wash off test may be also used determined mucoadhesive property of delivery system. mucoadhesion studies have been reported by using BIACORE integrated chip system method involves immobilization of polymer on tom the surface of the IC with the subsequent passage of the mucin solution over the same. This results in interaction of the mucin that of polymer surface the polymer mucin interaction is measure by an optical phenomenon called surface Plasmon resonance, which measures the change in refractive index when mucin binds on the polymer surface[35-37].

EVALUATION OF MICROSPHERES

Particle size and shape

Widely used to visualize micro particles are conventional light microscopy and scanning electron microscopy. Both techniques can be used to determine shape and outer structure of the micro particles. Particle size and distribution are determined by light microscopy, scanning electron microscopy, electron microscopy etc. Light microscopy provides a control over coating parameters in case of double walled microspheres. The scanning electron microscopy allows investigation of the microspheres surfaces after particles are cross sectioned and double walled system. Confocal lasers scanning microscopy is applied as a nondestructive visuallatization technique for micro particles and characterization of structures not only on the surface, but also inside the particles[38].

Electron spectroscopy for chemical analysis

The surface chemistry of microsphere can be determined using the electron spectroscopy for chemical analysis.

Density determination

The density of the microspheres can be measured by using a multivolume pychnometer.

Isoelectric point

The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity of different ph values ranging from 3 to 10 is calculated by measuring the time of particle movement over a distance of 1mm .using this data the electrical mobility of the particle can be determined. The electrophoretic mobility can be related to surface contained charge, ionisable behavior or ion absorption nature of microsphere.

Capture efficiency

The capture efficiency of the microsphere 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 monographic requirement the percent encapsulation efficiency calculated by following equation.

%entrapment=actual content/theoretical content ×100

Release studies

Release studies for microspheres in phosphate saline buffer ph 7.4, are carried out using rotating paddle apparatus or by using dialysis method. In case of the paddle apparatus the sample is agitated at 100rpm. The samples are taking at specific time intervals and are replaced by same amount of saline.

Angle of contact

The angle of contact is measure to determine the wetting property of micriparticulate carrier. It determines the nature of microspheres in terms of hydriphilicity or hydrophobicity. The angle of contact is measured at the solid/air/water interface. The angle of contact is measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 20 within a minute of deposition microspheres[39].

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