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MUCOADHESIVE MICROSPHERES: AN EMINENT ROLE IN CONTROLLED DRUG DELIVERY

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ABSTRACT

Mucoadhesion is simply known as interfacial force interactions between polymeric materials and mucosal tissues. In the last two decades mucoadhesive microspheres have received considerable attention for design of novel drug delivery systems due to their ability to prolong the residence time of dosage forms and to enhance drug bioavailability. 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, controlled and sustained release of drug from dosage form and specific targeting of drugs to the absorption site. 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.

Keywords: mucoadhesion, microspheres, controlled release, residence time.

INTRODUCTION

Since many years several kinds of diseases that may be acute or chronic diseases can be treated by using pharmaceutical dosage form like solutions, tablets, capsules, syrups, suspension, emulsion, ointments, creams, gels which can be used as orally, topically, or intravascular route. To get the proper therapeutic effect of these pharmaceutical dosage forms they should be administered several times a day, this results consequently undesirable toxicity, fluctuation in drug level and poor efficiency or therapeutic effect. Controlled release dosage form plays eminent role to overcome the problems which are discussed above. The most important example of controlled drug delivery system is mucoadhesive microspheres which can improve the therapeutic effect of administered drug. Also bioavailability of drug is also better than other conventional system because mucoadhesive microspheres remain close to the mucous membrane and absorption tissue. 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 healthcare system. The last two

decades in the pharmaceutical industry have witnessed an avant-garde interaction among the fields of polymer and material science, resulting in the development of novel drug delivery systems. 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 due 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 DDS with the absorbing membranes. It can be achieved by coupling bioadhesion characteristics to microspheres and developing novel delivery systems referred to as "mucoadhesive microspheres".[1]

Physiology of mucin

Mucus is produced in the eye, ear, nose and mouth. It also lines the respiratory, gastrointestinal and reproductive tracts. Its primary functions are the protection and lubrication of the underlying epithelium. Human cervical mucus, for instance, plays an integral role in both conception and contraception. It is essential to understand the structure and physical chemistry of mucus if the latter is to be exploited as a site for bioadhesive controlled drug release. Since the gastrointestinal tract is the primary site for drug absorption, the physiology of this site will be the focus of this discussion. The gelling properties which are essential to the function of mucus are the direct result of the glycoprotein present in the mucosal secretion. This glycoprotein is generally the same for various secretion sites within the body; however, specific and subtle biochemical differences have been identified. Mucus may be either constantly or intermittently secreted. The amount of mucus secreted also varies. The glycoproteinic component of mucus is a high molecular weight, highly glycosylated macromolecular system. This polydisperse natural polymer makes up between 0.5 and 5% of the fully hydrated mucus secretion. [10] The size of the intact molecule is approximately 1.8×10^6 , but the molecular weight of undegraded gastric mucin is as high as 4.5×10^7. These macromolecules are highly expanded random coils made up of monomeric glycoproteins which for humans range from $5.5 \times 1o^5$ in the stomach to $2.4 \times lo^5$ in the small intestine. Oligosaccharide branches are attached to 63% of the protein core while the remainder of

this core consists of unglycoslyated terminal regions. Human GI tract glycoproteins contain about 12-17% protein on a dry basis. The subunits of the macromolecule are coupled by peptide linkages and intramolecular cysteine-cysteine disulphide bridges. There are 34 disulphide bridges per molecule of rat goblet cell mucin, which has a molecular weight of 2 x 10^6, while porcine intestinal mucin has 28 bridges per molecule. Human mucin has a similar density of disulphide bonds. The protein spine of the macromolecule has about 800 amino acid residues. Sugar chains are attached at about every three residues along the glycosylated regions; this results in approximately 200 side chains per molecule. This molecule is resistant to proteolytic attack in the glycosylated regions only. [7]. Mucin glycoprotein is TO-90 wt% carbohydrate and there are between 2 and 20 residues per side chain. In addition to N-acetylgalactosamine, there are four other molecular components. These side chains contain alternating N-acetylglucosamine and galactose residues and have varying degrees of branching. Residues of ester sulphates appear at intermediate positions, while fucose and sialic acid occur at terminal endsl. At pH > 2.6, the sialic acid and sulphate residues are fully ionized; this confers a net negative charge to the molecule. Over 50% of the oligosaccharides contain acid groups. Thus, charge interactions may have a significant effect on the behaviour of mucus glycoproteins. The mucous gel covering the epithelium varies in thickness. In the human stomach, the mean thickness is 192 pm, while in the duodenum the thickness ranges from 10 to 400 pm [10]. Cohesion of the gel is dependent upon the glycoprotein concentration. In the gastrointestinal tract, mucus facilitates the passage of food and boluses through the alimentary canal. It also helps shield the epithelium from shear forces induced by peristaltic waves, and resists auto digestion. These functions are promoted by the constant secretion of mucus to replenish losses from turbulence and degradation. In response to an irritant, the amount of acidic side chains in the glycoprotein increases from 50 to 80%, making the macromolecule more negatively charged. The submucosal gland layer increases in depth and the number of goblet cells increases. The total content of non dialysable solids and pH also increase. In the GI tract, DNA and albumin thicken mucus in the diseased state. Mucosal irritation, such as exposure to alcohol or bile salts, elicits accelerated mucin release. Disease can significantly alter the nature and thickness of the mucus. This may lead to a change in the behaviour of the delivery system. Any drug

delivery system which is intended to adhere to the mucus epithelium will need to adapt to a substrate which varies in depth and consistency, and may also change biochemically. Hypersecretion, which is more common than hyposecretion during disease, increases the transit rate through the GI tract, and thus reduces the residence time of a mucoadhesive device. Thus, it is essential to consider the physiology of the system when optimizing the formulation of an adhesive controlled release device.

CLASSIFICATION OF MUCOADHESIVE POLYMERS

Mucoadhesion is defined as interfacial force interactions between polymeric materials and mucosal tissues. In the last two decades mucoadhesive polymers have received considerable attention for design of novel drug delivery systems due to their ability to prolong the residence time of dosage forms and to enhance drug bioavailability. Various administration routes, such as ocular, nasal, gastrointestinal, vaginal and rectal, make mucoadhesive drug delivery systems attractive and flexible in dosage forms development. Mucoadhesive polymers can be classified as,-

I. Traditional non-specific first-generation mucoadhesive polymers

First-generation mucoadhesive polymers may be divided into three main subsets, namely:

(1) *Anionic polymers:-* Anionic polymers are widely employed for its greatest mucoadhesive strength and low toxicity. These polymers are characterised by the presence of sulphate and carboxyl group that gives rise to net negative charge at PH values exceeding the pka of polymer.

Example:-polyacrylic acid (PAA) & its weakly cross linked derivatives,

Sodium carboxymethyl cellulose (NACMC) [30]

(2) *Cationic polymers:* - The most conveniently and widely used cationic polymer is chitosan which is produced by deacetylation of chitin. Chitin is a natural polysaccharide found predominantly in the shells of crustaceans such as crabs and shrimp, the cuticles of insects, and the cell walls of fungi. It is one of the most abundant biopolymers next to cellulose Most of the naturally occurring polysaccharides, e.g. cellulose, dextran, pectin, alginic acid, agar, agarose and carrageenans, are neutral or acidic in nature, whereas chitin and chitosan are examples of highly basic polysaccharides. The unique properties include

polyoxysalt formation, ability to form films, chelate metal ions and optical structural characteristics. Chitosan also have better mucoadhesive property.

(3) *Non-ionic polymers:-* These polymers are also used for its mucoadhesive property The example of Non-ionic polymer are,

Hydroxyethylcelullose (HEC), hydroxypropylcelullose (HPC, MM 300 kDa) Polyvinylpirrolidone 44000 (PVP, MM 44 kDa) and polyethylenglycole 6000 (PEG, MM 6 kDa)

II.Novel second-generation mucoadhesive polymers:

The major disadvantage in using traditional nonspecific mucoadhesive systems (first generation) is that adhesion may occur at sites other than those intended. Unlike first-generation non-specific platforms, certain second-generation polymer platforms are less susceptible to mucus turnover rates, with some species binding directly to mucosal surfaces; more accurately termed ‘‘cytoadhesives”. Furthermore as surface carbohydrate and protein composition at potential target sites vary regionally, more accurate drug delivery may be achievable.

Examples:-

1) ***Lectins: -*** Lectins are naturally occurring proteins that play a fundamental role in biological recognition phenomena involving cells and proteins. For example, some bacteria use lectins to attach themselves to the cells of the host organism during infection. Enhancement of mucosal delivery may be obtained through the use of appropriate cytoadhesives that can bind to mucosal surfaces. The most widely investigated of such systems in this respect are lectins.

2) ***Thiolated polymers: -*** Thiolated polymers (thiomers) are a type of second generation mucoadhesive derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum. Examples re Chitosan–iminothiolane (250-fold improved mucoadhesive properties), Polyacrylic acid–cysteine (100-fold improved mucoadhesive properties), Polyacrylic acid–homocysteine (Approximately 20-fold improved mucoadhesive properties), and Chitosan– thioglycolic acid (Tenfold improved mucoadhesive properties), Chitosan–thioethylamidine (Ninefold improved mucoadhesive properties) and Alginate–cysteine (Fourfold improved mucoadhesive

MUCOADHESION

Due its relative complexity, it is likely that the process of mucoadhesion cannot be described by just one of these theories. In considering the mechanism of mucoadhesion, a whole range 'scenarios' for in-vivo mucoadhesive bond formation are possible. These include:

A). Dry or partially hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates administered into the nasal cavity).

B). fully hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates of many 'First Generation'mucoadhesives that have hydrated in the luminal contents on delivery to the lower gastrointestinal tract).

C). Dry or partially hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically tablets or patches in the oral cavity or vagina).

D). fully hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically aqueous semisolids or liquids administered into the oesophagus or eye).

It is unlikely that the mucoadhesive process will be the same in each case. In the study of adhesion generally, two steps in the adhesive process have been identified [16], which have been adapted to describe the interaction between mucoadhesive materials and a mucous membrane. [11, 13]

Step 1 —Contact stage: An intimate contact (wetting) occurs between the mucoadhesive and mucous membrane.

Step 2 —Consolidation stage: Various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion.

THEORIES ON MUCOADHESION [4, 5]

Various kinds of theories are there which can explain the mechanism of mucoadhesion they are discussed below,

Electronic theory: - Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determine the mucoadhesive strength

Adsorption theory:-According to the adsorption theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished.

1. Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because their high strength may result in permanent bonds
2. Secondary chemical bond having many different forces of attraction, including electrostatic forces, Vander Waals forces, and hydrogen and hydrophobic bonds

Wetting theory: - The ability of adhesive to spread spontaneously on mucin influences development of intimate contact between the mucoadhesive and mucin, and consequently influences the mucoadhesive strength. The thermodynamic work of adhesion is function of the surface tension of the surface in contact as well as the interfacial tension. A small value of interfacial tension would mean a more intimate contact between the two surfaces.

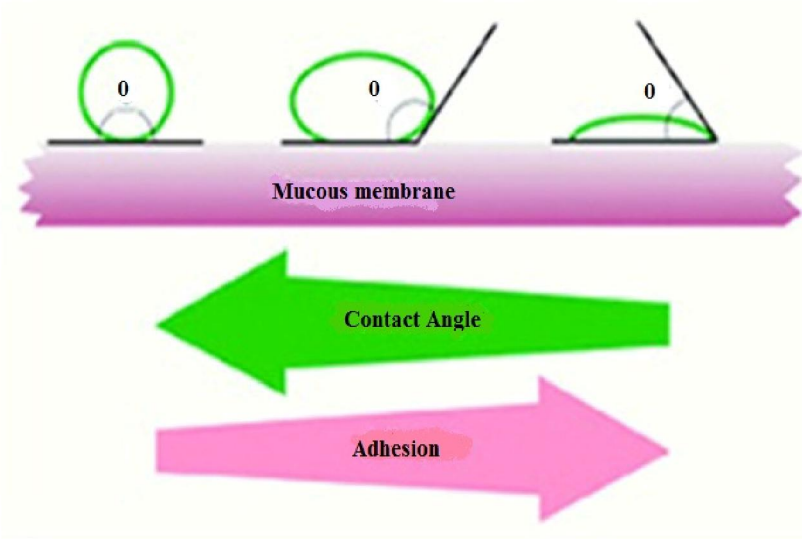

Figure no.1: Schematic diagram showing influence of contact angle between device and Mucous membrane on bioadhesion

Diffusion theory: - According to diffusion 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 chains penetrate the mucus depends on the diffusion coefficient and the time

of contact. This diffusion coefficient, in turn, depends on the value of molecular weight between cross-links and decreases significantly as the cross-linking density increases.

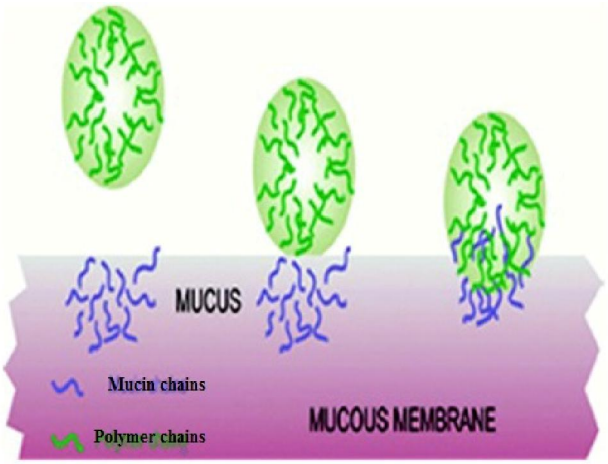

Fig no.2-Secondary interactions resulting from inter diffusion of polymer chains of bioadhesive device and of mucus

Fracture theory: - Fracture theory attempts to relate the difficulty of separation of two surfaces after adhesion.Fracture theory equivalent to adhesive strength is given by:

$$G = (E/L)\, l\, h$$

Where E = Young's modulus of elasticity is the fracture energy and

L = critical crack length when two surfaces are separated [Figure

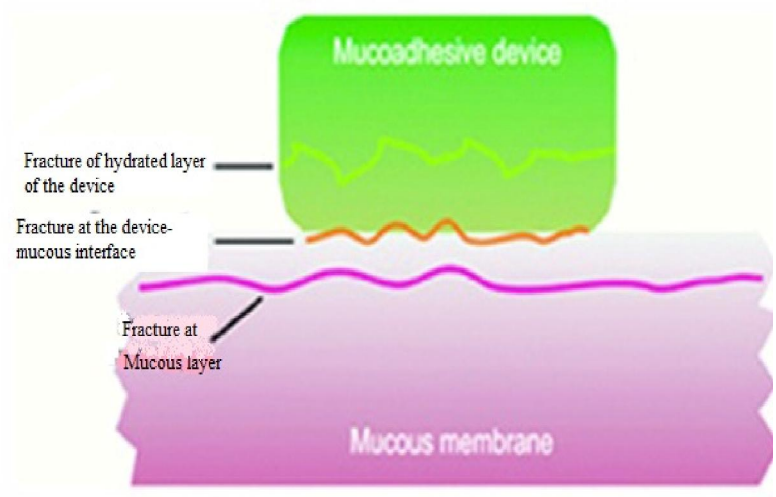

Fig no.3 - Regions where the mucoadhesive bond ruptures can occur.

Electronic theory: - Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determine the mucoadhesive strength

TYPES OF MICROSPHERES

Mucoadhesive microspheres:-Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bio -adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action. [26]

Magnetic microspheres:-This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different type are,

Therapeutic magnetic microspheres: Are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.6

Diagnostic microspheres: Can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.

Floating microspheres:-In this type of microspheres the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The release rate of drug is slow at the desired rate, if the system is floating on gasteric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances dose dumping. Also one most important thing is to prolonged therapeutic effect and therefore reduces dosing frequencies.

Radioactive microspheres:-Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest.

Polymeric microspheres:-The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric

METHODS OF PREPARATION OF MICROSPHERES [2, 3]

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). Microspheres are sometimes referred to as microparticles.

Various methods of preparation of microspheres are as follows,

Emulsion solvent evaporation technique:

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0 .2 % sodium of pvp as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24hrs.12 Aceclofenac microspheres were prepared by this technique.

Emulsion-solvent diffusion technique:

To improve the residence time in colon floating microparicals are prepared by this technique. The mixture of ethanol and dichloromethane (1:1) and then drug polymer mixture dissolved in mixture of ethanol and dichloromethane and then the mixture was added dropwise to sodium lauryl sulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microspheres were washed and dried in a dessicator at room temperature. The following microparticles were sieved and collected.

Emulsion cross linking method:

In this method drug was dissolved in aqueous gelatine solution which was previously heated for 1 hr at 40 0C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 oC, results in w/o emulsion then further stirring is done for 10 min at 15 0C. Thus the produced microspheres were washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100mL of 10mm

glyciene solution containing 0.1%w/v of tween 80 at 37 0 C for 10 min to block unreacted glutaraldehyde.18 Examples for this technique is Gelatin A microspheres. [3]

Multiple emulsion method:

Oral controlled release drug delivery of indomethacin was prepared by this technique. In the beginning powder drug was dispersed in solution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethyl acctate. The primary emulsion was then re-emulsified in aqueous medium. Under optimised condition discrete microspheres were formed during this phase.

Co-acervation method:

Co-acervation thermal change: Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80 0C by heating. Then the drug was finely pulverised and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twice with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule.1 Co-acervation non solvent addition: Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propyl isobutylene in closed beaker with magnetic stirring for 6 hr at 500 rpm and the drug is dispersed in it and stirring is continued for 15 mins. Then phase separation is done by petroleum benzoin 5 times with continuous stirring.1After that the microcapsules were washed with n-hexane and air dried for 2 hr and then in oven at 50oc for 4 hr. [3]

Ionic gelation:

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. 25 % (w/v) of diclofenac sodium was added to 1.2 % (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added drop wise to a solution containing Ca2+ /Al3+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 hr for internal gellification followed by filtration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH.

Spray drying technique:

This was used to prepare polymeric blended microsphere loaded with ketoprofen drug. It involves dispersing the core material into liquefied coating material and then spraying the

mixture in the environment for solidification of coating followed by rapid evaporation of solvent.4 Organic solution of poly (epsilon-caprolactone) (PCL) and cellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microspheres. This is rapid but may lose crystalinity due to fast drying process.

EVALUATION PARAMETERS

Various evaluation parameters are there which are enlisted below,

- Ø Entrapment Efficiency
- Ø Swelling index
- Ø Stability studies
- Ø Density determination
- Ø Bulk density
- Ø Angle of contact
- Ø In vitro mucoadhesion test
- Ø In vitro drug release studies
- Ø In situ Bioadhesivity Studies

ADVANTAGES [1]

1. Microspheres provide constant and prolonged therapeutic effect.
2. Reduces the dosing frequency and thereby improve the patient compliance.
3. They could be injected into the body due to the spherical shape and smaller size.
4. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
5. Microsphere morphology allows a controllable variability in degradation and drug release.

LIMITATION [1]

Some of the limitations were found to be as follows

1. The release rate from one dose to another may be different.
2. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.

3. Food and the rate of transit though gut may affect the release rate of the controlled release dosage form
4. Dosage forms of this kind should not be crushed or chewed.

APPLICATION

1. Proteins, hormones and peptides are released over extended period of time.
2. Microspheres can be used as carrier for delivery of Vaccine for treatment of diseases like diphtheria, hepatitis, ricin toxoid, birth control, influenza.
3. Microspheres are used for Gene therapy with DNA plasmids and also as a carrier for delivery of insulin.
4. Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra-arterial/ intravenous application.
5. Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
6. Used in isolation of antibodies, cell separation and toxin extraction by affinity Chromatography.
7. Microspheres play an important role in diagnosis of infectious diseases like bacterial, viral, and fungal.

CONCLUSION

Mucoadhesive microspheres drug delivery system plays an eminent role by keeping the advantage of controlled and sustained release action. These microspheres are also plays major role as a carrier of various delivery drugs and vaccines. These carrier systems will increases the residence time of the drug in gastrointestinal tract. Because of the increase in residence time the absorption of the administered drug will be extended and therapeutic effect will become in controlled manner. Mucoadhesive microspheres are better alternative for non-invasive delivery of potent peptides and protein drug delivery.

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