WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 6, 1368-1385. Review Article ISSN 2277– 7105

CHITOSAN BASED MUCOADHESIVE MICROSPHERE: VERSATILE CARRIER FOR NASAL DRUG DELIVERY SYSTEM

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Article Received on
20 June 2014,

Revised on 15 July 2014,
Accepted on 10 August 2014

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ABSTRACT

The nasal route is one of the most permeable and highly vascularised sites for drug administration ensuring rapid absorption and onset of action. The interest in intranasal delivery of drugs as a non-invasive is increased. In this review we have discussed advantages, disadvantages, mechanism of action and factor affecting the permeability of drugs or biomolecule through nasal mucosa of nasal drug delivery system in local delivery, systematic delivery of the drug. We are also discussed here relevant aspects of biological, physicochemical and pharmaceutical factors of nasal cavity that must be considered during the process of discovery and development of new drugs for nasal delivery as well as in there incorporation into appropriate nasal Pharmaceutical formulations. In recent years, Mucoadhesive microspheres have been developed for oral, buccal, nasal, ocular, rectal and vaginal for either systemic or local effects. The principles underlying the development of Mucoadhesive microsphere and evaluation carried out on these systems are reviewed here.Much has been investigated and much more are to be investigated for the recent advancement of nasal drug delivery system.

KEY WORDS: Nasal route, Permeability,Mucoadhesive Microsphere.

INTRODUCTION

The administration of drugs via nose is not a novel approach for drug delivery. In ancient time depending on the therapeutic intent, nasal drug delivery was used for local treatment or systemic action or for acute or chronic treatment[1].Nowadaysnasal drug delivery system has been carried out better systemic bioavailability via nasal route as compared oral drug administration.Nasal drug delivery system is also suitable for restrain and hindrance blood brain barrier by which the drug can be easily delivered in CNS.[2,3]

Physiological Aspect of the Nose

The nasal passage, which runs from the nasal vestibule means, nasal valve to the nasopharynx, has a depth of approximately 12-14cm. The lining of nasal cavity possesses many advantages as a site for drug delivery such as a large surface area for absorption with a sub-epithelial layer that is highly vascularized, and rich in mucus gland and goblet cell, ease of administration and applicability form long-term treatment. An important consideration in nasal drug delivery is the effect of drugs and additives administered intranasally on nasal ciliary function and many drugs administered. Nasal mucociliary clearance is one of the most important limiting factors for nasal drug delivery. It severely limits the time allowed for drug absorption to occur. However, mucoadhesive preparations have been developed to increase the contact time between the dosage form and mucosal layers of nasal cavities, thus enhancing drug [4,5]

Advantages of nasal drug delivery system[6,7,8,9]

1. Provides straightaccess of drug into systemiccirculation.
2. The nasal mucosa withnumerous microvilli is highly vascularised with large and fenestratedcapillaries facilitating rapid absorption.
3. Avoidance of first pass elimination, gut wall metabolism anddestruction in gastrointestinal tract.
4. Results in rapid absorption and onset of effect.
5. Results in higher bioavailability thus use lower doses of drug.
6. Easily available, non-invasive route.
7. Larger drug molecules can be improved their bioavailability by means of absorption enhancer.

Limitations of nasal drug delivery system[9, 10]

1. Volume that can be delivered into nasal cavity is limited to 25–200 µl.
2. High molecular weight compounds cannot be delivered through this route (mass cut off ~kD)
3. Sometimes absorption enhancers may disrupt and even dissolve the nasal membrane in high concentration.
4. Cause irritation of nasal mucosa by drugs.
5. Normal defence mechanism like mucociliary clearance is one of the most important Factors.

Mechanism approach for nasal drug absorption[10, 11, 12]

Passage of drug via the mucus is considered as the first step in the drug absorptionfrom the nasal cavity. Uncharged as well as small particles easilypass through mucus. However, charged or large particlesshowmore difficulty to cross. Several mechanisms have beenproposed but the following two mechanisms have been consideredpredominantly.
(NGN swami)

The first mechanism of drug absorption involves an aqueous route of transport also called as the Paracellular route which is slow and passive. In this route there is an inverse log-log correlation between the molecular weight of water-solublecompounds and intranasal absorption. Higher molecularweight(greater than 1000 Daltons)drugs shown poor bioavailability.

The second mechanism includes transport of drug through alipoidalroute also called as the transcellular process. Transcellular route isresponsible for the transport of lipophilic drugs that show arate dependency on their lipophilicity. Cell membrane may becrossed by drugs by an active transport route *via* carriermediatedmeans or transport through the opening of tightjunctions.Example: Chitosan(linear cationic polysaccharide) opens tight junctions between epithelial cells and enhanced absorption.

Mucoadhesive Microsphere as a Nasal Drug Delivery System[13, 14]

Microspheres represent an important part of nasal drug delivery systems by asset of their small size and proficient carrier capacity. Microsphere are solid spherical particles included range(insize) from 1-1000μm. Microspheres are, in strict sense, spherical empty particles. They are biodegradable innature,whichare free flowing powders consisting of proteins or synthetic polymers.There are two types of microspheres; microcapsules and micrometrics,Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersing throughout the microspheres matrix. Solid biodegradable microspheres incorporating a drug dispersed or dissolved through particle matrix have the potential for the controlled release of drug. They are made up of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products. Mucoadhesive microsphereshave advantages like efficient absorption and due to high surface to volume ratio enhanced bioavailability of the drugs, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.

All types of microspheres water insoluble in nature but absorb water into the matrix of sphere that have been used as nasal drug delivery system, resulting in swelling of the spheres and the formation of a gel. The basic materials in the microspheres have been starch, dextran, albumin and hyaluronic acid, and the bioavailability of several peptides and proteins has been improved in different animal models. Also, low-molecular weight drugs have been successfully delivered in microsphere preparations. The residence time in the nasal cavity is significantly increased for microspheres compared to solutions. Microspheres also put forth a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cells. The nasal route for systemic drug delivery has mainly been investigated with large hydrophilic peptides and proteins in mind, while other type of drugs has also been investigated. Different types of absorption enhancers used to overcome the trouble of low absorption.On the basis absorptions two type of the polymers used in microspheres-

1. Mucoadhesive
2. Bioadhesive

Mucoadhesion is defined as adhesion of matter to a mucus layer for an extended period of time by interfacial force and mucoadhesive agent is a substance that adheres to mucus. The term bioadhesion is less specific and can be used to signify adhesion to any biological surface. Many investigations have since shown positive results for nasal delivery by mucoadhesivemicroparticles,*i.e.*, micron-sized particles of drug and excipients, in comparison with liquid formulations or the pure drug Several mucoadhesive polymers, for example degradable starch microspheres, cellulose,carbomer, alginate and the popular, cationic polymer chitosan, have been investigated.

“Bioadhesion”in simple terms can be described as the attachment of a synthetic or biological macromolecule to a biological tissue. An adhesive bond may form with epithelial cell layer, the continuous mucus layer or a combination of the two. The term “mucoadhesion” is used specifically when the bond involves mucous coating and an adhesive polymeric device. The use of dry-powder formulations containing bioadhesive polymers for nasal administration of peptides and proteins water- insoluble cellulose derivatives were mixed with insulin and the powder mixture was installed into the nasal cavity.

Need of Mucoadhesion[15]

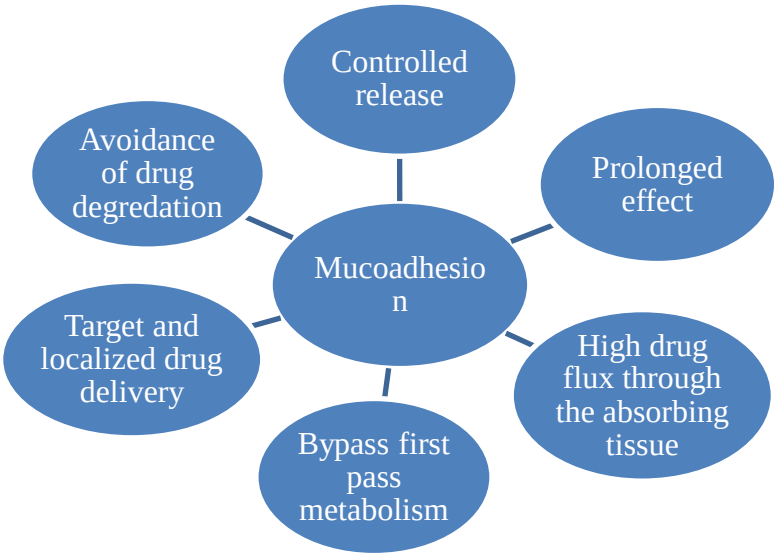

FIG .1 FLOW CHART OF NEED OF MUCOADHESION

Mechanism of Mucoadhesion[16,17]

The process of mucoadhesion nasal administration relates to the interaction between the mucoadhesive polymer and the mucus secreted by the sub-mucosal glands.The sequential events that occur during the mucoadhesion include the proper wetting and swelling of the polymer, and intimate contact between the polymer and the nasal mucosa. Then, the swelled mucoadhesive polymer penetrates into the tissue crevices followed by the interpenetration between the polymer chains and protein chains of the mucus,to obtain sufficient absorption of drugs, first, the formulation should spread well on the nasal mucosa. Therefore,the spreadability is the very important for MucoadhesiveFormulation, so accomplish the flowability and wettability for the solid mucoadhesiveformulation.A complete perceptive ofhow certain macromolecules attach to a mucus surface is not yet accessible, 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 mechanismofmucoadhesion.

Electronic Theory

This theory is based on the assertion that both mucoadhesive and biological materials having opposing electrical charges. Therefore, 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 determines the mucoadhesive strength.

e.g.Interaction between positively charged polymers Chitosan and negatively charged mucosal surface which becomes adhesive on hydration and provides an intimate contact between a dosage form and absorbing tissue.

Absorption Theory

According to this theory, after an initial contact between two surfaces, the material adheres because of surface force acting between the atoms in two surfaces. Basically two types of chemical bonds resulting from these forces can be well-known as primary chemical bonds of covalent nature and Secondary chemical bonds having many different forces of attraction, like electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.

Diffusion Theory

According to this theory, a semipermanent adhesive bond is created by the polymer chains and the mucus mix. The depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact. The diffusion coefficient in terms depends on the value of molecular weight between crosslinking and decreases as the cross linking density increases.

Wetting Theory

This theory suggests that 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 substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive among the substrate surface.

Cohesive Theory

The cohesive theory postulates that the Phenomenon of Bioadhesion is mainly due to intermolecular interaction amongst like molecule. Based upon these theories, the process of bioadhesion can broadly be classified into two categories namely chemical (electron and absorption theory) and physical (wetting, diffusion and cohesive theory).

Advantages of Mucoadhesive Microspheres[18]

There are some advantages of Mucoadhesive microsphere shown in figure-

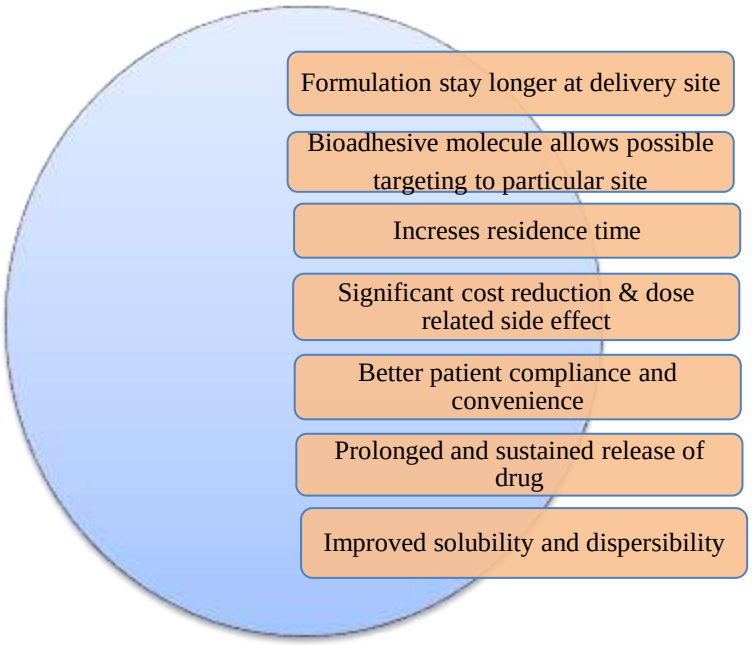

Fig. 2 Flow Chart Of Advantage Of Mucoadhesive Microsphere

Polymers used in the formulation of mucoadhesive microspheres

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, joined 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. Mucoadhesive polymers that adhere to the mucin–epithelial surface can be conveniently divided into three broad classes.[19,20, 21, 22]

1. Polymers that become sticky when they put in water and owe their mucoadhesionto stickness.
2. Polymers that adhere through nonspecific, noncovalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
3. Polymers that bind to specific receptor site.

   There are following polymers which used in formulation of mucoadhesive microsphere

Hydrophilic polymers

The polymers which belong to this category are easily soluble in water. Material developed with these polymers swell when put into water with dissolution of the matrix. the poly electrolytes shows greater mucoadhesive property as compared to neutral polymer. Anionic polyelectrolytes, e.g. poly (acrylic acid) and carboxymethyl cellulose usedfor designing

mucoadhesive delivery systems because of their ability to exhibit strong hydrogen bonding with the mucin of mucosal layer[23,24]Chitosanan example of cationic polyelectrolyte, which has been extensively used fordevelop mucoadhesive polymer due to its good biocompatibility and biodegradable properties. Chitosan undergoes electrostatic interactions with the negatively charged mucinchains thereby exhibitingmucoadhesive property. The ionicpolymers may be used to develop ionic complex with the counter-ionic drug molecules so as to have adrug delivery matrix exhibiting mucoadhesive property. Non-ionic polymers, e.g. poloxamer,hydroxypropyl methyl cellulose, methyl cellulose, poly (vinyl alcohol) and poly (vinyl pyrrolidone) havealso been used for mucoadhesiveproperties.

Hydrogels

Hydrogels defined as three-dimensionallycrosslinkedpolymer chains which have the capacity to hold water in its porous structure is mainly due to the presence of hydrophilic functional groups such as amino and carboxyl groups.it is prepared by the condensation reaction of poly acrylic acid and sucrose which indicates an increment in the mucoadhesive property with the increase in the crosslinking density and was traits to increase in the poly (acrylic acid) chain density per unit area.Acrylateshave capacity to deliver peptide bioactive agents to the upper small intestine region without any change in the bioactivity of the peptides.

Thiolated polymers

Thiolated polymers (thiomers) are secondgenerationmucoadhesive derived from hydrophilic Polymers such as polyacrylates, chitosan ordeacetylatedgellan gum. Examples are Chitosaniminothiolane (250-fold improved mucoadhesiveproperties), Polyacrylic acid–cysteine (100-foldimproved mucoadhesive properties), Polyacrylicacid–homocysteine (Approximately 20-foldimproved mucoadhesive properties), Chitosan-thioglycolic acid (Tenfold improved mucoadhesiveproperties), Chitosan–thioethylamidine (Ninefoldimproved mucoadhesive properties) and Alginate–cysteine (Fourfold improved mucoadhesiveproperties) etc. The presence of thiol groups allowsthe formation of covalent bonds with cysteine-richsub domains of the mucus gel layer, leading toincreased residence time and enhanced bioavailability. In this respect thiomersimitate thenatural mechanism of secreted mucus glycoproteinsthat are also covalently anchored in the mucus layer by the formation of disulphide bonds. Whilst firstgenerationmucoadhesive platforms are facilitated vianon-covalent secondary interactions, the covalentbonding mechanisms involved in second- generationsystems lead to interactions that are less susceptibleto changes in ionic

strength and/or the pH. Moreoverthe presence of disulphide bonds may significantlyalter the mechanism of drug release from the deliverysystem due to increased rigidity and crosslinkingmechanism is more typical, whereas in firstgenerationpolymers anomalous transport of API intobulk solution is more common.Chitosan [2-amino-2-deoxy-(1→4)-β-d-glucopyranan] is a linear cationic polysaccharide which is obtained by a process of deacetylation from chitin, an abundant structural polysaccharide in shells of crustacea, such as lobsters, shrimps, and crabs. Due to the NH groups resultant from the deacetylation process, chitosan is insoluble at neutral and alkaline pH. However, it can form water-soluble salts with inorganic and organic acids including glutamic acid, hydrochloric acid, lactic acid, and acetic acid. Toxicity tests have revealed that the LD50 of chitosan in mice exceeds 16 g/kg. Because of its low cost, biodegradability, and biocompatibility, chitosan has been increasingly applied as pharmaceutical excipients in oral, ocular, nasal, implant, parenteral, and transdermal drug delivery.[25, 26]Chitosan and its derivatives have been shown to be active in enhancing the intranasal drug absorption due to their excellent mucoadhesive properties. It was also confirmed that coating micro- and nanoparticulates with chitosan could improve drug adsorption to mucosal surfaces.[27]

Lectin-based polymers

Lectins are proteins which have capacity to reversibly bind with specific sugar carbohydrates residues and are found in both animal and plant kingdom. The affinity of lectins towards sugar or carbohydrate residue 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 system.

Method of preparation of Chitosan basedmucoadhesive microsphere

There are different methods used for microspheres preparation depends on particle size, route of administration, duration of drug release and all above characters related to rpm, method of cross linking, drug of cross linking, evaporation time, co-precipitation etc. The various methods of preparations are

Preparation of Microspheres by cross-linking method-[28]

This method used the reactive functional amine group of Chitosan to cross-link with aldehyde groups of the cross-linking agent. In this method, the natural polymer like chitosan is dissolved in non- aqueous medium and formed water in oil (w/o) combination. In the second

step of formulation,cross-linking of the dispersed globule is carried out. The chemical cross linking agents used include glutaraldehyde, formaldehyde, diacid chloride etc. this method is Schematically represented in FIG.3

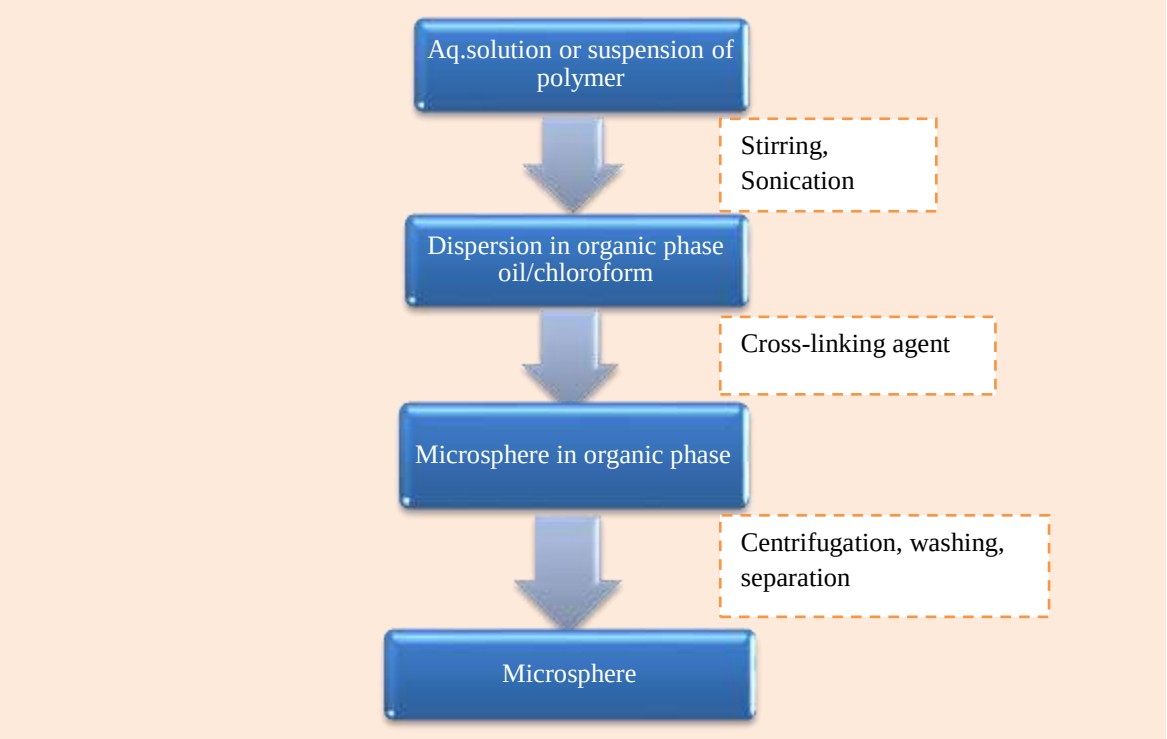

Fig. 3 Flow Chart Of Emulsion Cross-Linking Method

Preparation of Ethylcellulose Microspheres

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 suit able 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.

Ionic Gelation method

In the ionic gelation method, Chitosan is dissolved in aqueous solution(acidic in nature) to obtain the cation of Chitosan. This solution is then added dropwise under constant stirring to polyanionic TPP solution.Due to the complexation between oppositely charged species, Chitosan undergoes ionic gelation and precipitates to form spherical particles.[29]

Phase separation /Coacervation technique

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.[30]

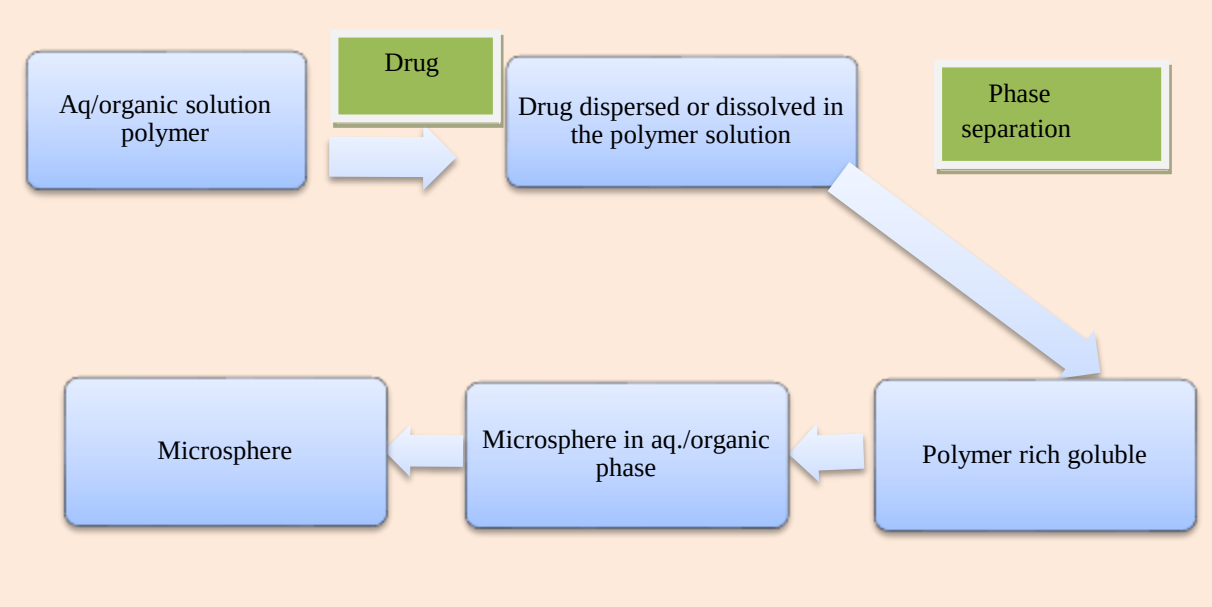

Fig. 4 Flow Chart Of Phase Separation Method

Spray Drying[31]

In Spray Drying method, the polymer is firstly dissolved in a suitable volatile organic solvent such asdichloromethane, 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 astream 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[32]

The processes are carried out in a liquidmanufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immisciblewith the liquid manufacturing vehicle phase. A corematerial to be microencapsulated is dissolved ordispersed in the coating polymer solution. Withagitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain theappropriate size microcapsule. The mixture is thenheated if necessary to evaporate the solvent for thepolymer of the core material is disperse in thepolymer solution, polymer shrinks around the core. Ifthe core material is dissolved in the coating polymersolution, matrix – type microcapsules are formed.The core materials may be either water soluble orwater in soluble materials. Solvent evaporationinvolves the formation of an emulsion betweenpolymer solution and an immiscible continuousphase 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 gelatin prepared by complex coacervation were made.

Wet Inversion Technique[33]

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

Drug Release Kinetics[34]

Release of drug is an important consideration in case of microspheres. Many theoretically possible mechanisms for the release of drug from the microsphere may be as follows:

1. Liberation of the drug due to polymer erosion or degradation.
2. Self diffusion of drug through the pore of the microspheres.
3. Release of the drug from the surface of the polymer.
4. Pulsed delivery initiated by the application of an oscillating or sonic field.

Evaluation of Mucoadhesive Microsphere

There are following method used for the evaluation of mucoadhesive microsphere

Particle size, shape and morphology[35]

The size of the prepared microspheres can bemeasured by the optical microscopy method using acalibrated stage micrometer for randomly selectedsamples of all the formulations.

Optical microscopy

This method is used to determine particle size ofmicrospheres by using optical microscope (MeizerOPTIK) The measurement is done under 45x (10x eyepiece and 45x objective) and100 particles arecalculated.[36]

Surface topography by Scanning ElectronMicroscopy (SEM)

SEM of the microspheres shows the surfacemorphology of the microspheres like their shape andsize.Scanning electron microscopy (SEM) is determinedby the method SEM. In this method microspheres aremounted directly on the SEM sample slum with thehelp of double sided sticking tape and coated withgold film under reduced pressure. Scanning Electronphotomicrographs of drugloaded microspheres aretaken. A small amount of microspheres s spread ongold stub. Afterwards, the stub containing the sampleis placed in the Scanning electron microscopy (SEM).A Scanning electron photomicrograph is taken at anacceleration voltage of 20KV and chamber pressure of 0.6 mm Hg.[37,38]

Particle Size Analysis

The particle sizes and particles size distributions arefurther analyzed by using dynamic light scatteringtechnique, Microspheres are dispersed into 100 ml ofwater and sonicated for 1 min to removeagglomerations. The mean volume diameter (Vd) is recorded and polydispersity is determined by theSPAN factor. A high value of SPAN indicates a widedistribution in size and a high polydispersity.

Entrapment Efficiency[39]

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

The percent encapsulation efficiency is calculated using following equation-

% Entrapment = Actual content/Theoretical content x 100

Surface Charge Study

From photon correlation spectroscopy data the surface charge (zeta potential) of the mucoadhesive microspheres can be determined. The surface charge can be determined by relating measured electrophoretic mobility into zeta potential with in-built software based on the Helmholtz– Smoluchowskiequation[40] Zeta potential is an indicator of particle surface charge, which can be used to predict and control the adhesive strength, stability, and the mechanisms of mucoadhesion. Process of mucoadhesion involves interactions between the mucus and mucoadhesive polymers, and is influenced by their structure including their charge. Measurement of zeta potential of microspheres and mucus helps to predict electrostatic interactions during mucoadhesion.[41]

Swelling Index[42]

Swelling index illustrate the ability of the mucoadhesive microspheres to get swelled at the absorbing surface by absorbing fluids available at the site of absorption ,which is a primary requirement for initiation of mucoadhesion. The percent swelling value can be determined using following equation. Percent swelling = DT - D0 / D0 × 100 Where, D0 = weight of dried microspheres DT = weight of swelled microspheres

***In- Vitro* Release Study[43]**

Standard IP/BP/USP dissolution apparatus is used to study *in-vitro* release profile in the dissolution media that is similar to the fluid present at the absorption site as per monograph, using rotating basket or paddle type dissolution apparatus.

***Ex-Vivo* Mucoadhesion Study[44]**

The mucoadhesive property of the microspheres is evaluated on goat's intestinal mucosa by using phosphate buffer, as per monograph. Weighed microspheres are spread onto wet rinsed tissue specimen and immediately thereafter the slides are hung onto the arm of a USP tablet disintegrating test machine with suitable support at 370C. The weight of microspheres leached out at different intervals is measured. The % mucoadhesion is calculated by the following equation.% Mucoadhesion = Wa-W1/Wa *100

CONCLUSION

With advantages such as mucoadhesion, an increase in the residence time of the polymer, penetration enhancement, and enzymatic inhibition, mucoadhesive polymers will

undoubtedly be utilized for the nasal delivery of a wide variety of therapeutic compounds. Chitosan polymer has enormous potential for the delivery of therapeutic macromolecules, genes, and vaccines.With recent advancements in the fields of biotechnology and cytoadhesion, here discussed various methods for preparation and evaluation of chitosan microsphere which could help to design more and better functionalized chitosan-based carrier systems. It believe that there will be both academic and industrial efforts to explore this new area of nasal drug delivery, and it might not be too far-fetched to envisage more and more nasal products that employ mucoadhesive polymers.

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