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A OVERVIEW OF NASAL TO BRAIN DRUG DELIVERY SYSTEM BY MUCOADHESIVE MICROSPHERES

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ABSTRACT
Use of the nasal route for the delivery of challenging drugs such as small polar molecules, vaccines, hormones, peptides and proteins has created much interest in nowadays. Due to the high permeability, high vasculature, low enzymatic environment of nasal cavity and avoidance of hepatic first pass metabolism are well suitable for systemic delivery of drug molecule via nose. The unique relationship between nasal cavity and cranial cavity tissues in anatomy and physiology makes intranasal delivery to the brain feasible. An intranasal delivery provides some drugs with short channels to bypass the blood–brain barrier (BBB), especially for those with fairly low brain concentrations after a routine delivery, thus greatly enhancing the therapeutic effect on brain diseases. In the past two decades, a good number of encouraging outcomes have been reported in the treatment of diseases of the brain or central nervous system (CNS) through nasal the paper also includes. The different types of batters which affects the delivery and how to overcome it low bioavailability low membrane transport enzyme degradation etc physicochemical propertiesthats overcome by prodrug inoveative formulation absorption enhancer etc drug are delivered through the verious type of divices to nose to reach brain.

KEYWORDS: blood–brain barrier (BBB), central nervous system (CNS).

INTRODUCTION[1,2]

Routes encounter acidic or enzymatic degradation and Drugs are delivered to the systemic oral, parenteral (intravenous, intramuscular), and in most cases, drugs administered via these circulation via several routes, such as may undergo excessive first-pass effect (hepatic metabolism) following administration. Due to these factors, effective doses of drugs sometimes may not reach the systemic circulation, resulting in ineffective treatment. It is therefore required to explore either alternate routes or specialized delivery technologies that can result in improved and effective drug delivery options. The nasal route of drug delivery is one such alternate route that provides access to highly vascularized mucosa, which can be exploited as an interesting site for local drug delivery, systemic drug delivery, and targeted drug delivery.

Nose to Brain approach is a great area of interest for direct transport pathway of drugs in nose to brain through olfactory and trigeminal nerve cells through nose they can bypassing the BBB and enter brain directly. Olfactory region of the nasal mucosa is direct connection between nose and brain explored for CNS acting drugs. Improvement in bioavailability of some drugs and therapeutic proteins and peptides was reported). For nose to brain delivery, drugs need to permeate the BBB from the circulation. To achieve this, drug or Prodrug is absorbed through active and passive transport to cross the tight junctions of the BBB. Drug applied in nasal pathway is directly reaches to the brain either by direct transport from olfactory region to the brain and from blood to brain or CSF).

The olfactory region, next to the respiratory region in which, drug is directly absorbed into the brain by different mechanisms including transcellular, paracellular, olfactory and trigeminal neural pathways. The olfactory region of nasal mucosa contains olfactory cells, which extend up to cranial cavity. In nose to brain approach drug formulation on nasal instillation comes in contact with nasal mucosa and it is rapidly transported directly into the brain. Bypassing the BBB and achieving very rapid CSF levels. Some amount of administered drug is reaches to systemic circulation by respiratory region and some amount of drug is lost to nasal associated lymphoid tissue. The hydrophobic (lipid soluble) molecules is rapidly enter to the blood stream from nasal mucosa and subsequently reach the CNS by crossing the BBB. But, Maximum pharmaceutical drug is

hydrophilic (water soluble), this drug is a rate limiting barrier for targeting and highly lipid soluble drug molecules show better targeting ability due to higher partition coefficient (higher lipophilicity). Hydrophilic drug molecules is also cross the nasal mucosa when, nasal mucosa is break down due to local injury). In the recent years, most of drugs and Proteins and Peptides is delivered efficiently by using Nose to Brain Delivery. This strategy is useful to treat variety of CNS disorders including, Brain tumors, Parkinson disorder, MultipleSclerosis, Alzheimer disorder, Epilepsy and Psychiatric disorders). This is all the possible pathways for drug can reach brain after nasal administration are predominately either by the olfactory or trigeminal region or through systemic circulation.

Advantages[3]

1) The nasal bioavailability for smaller drug molecules is good.
2) Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
3) Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
4) Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
5) Drug degradation that is observed in the gastrointestinal tract is absent.
6) Hepatic first pass metabolism is avoided.
7) Rapid drug absorption and quick onset of action can be achieved.
8) The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

Limitations[4,5]

1) The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
2) Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
3) Nasal cavity provides smaller absorption surface area when compared to GIT.
4) There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
5) Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.

Anatomy[2]

The nasal septum divides the human nose into two equal symmetrical halves. The posterior part of the nasal cavity is called the nasopharynx, and each symmetrical half opens to the environment. Both halves of the nasal cavity consist of the following four regions.

Vestibule

Is not very highly vascularized and permeability of the drugs via this region is very poor. Atrium: Vascularization in this part of the nasal cavity is low, which results in moderate permeability of drugs.

Respiratory Region

This part of the nasal cavity is highly vascularized and therefore the permeability of drugs from this region is good.

Olfactory Region

Is highly vascularized, which results in high permeability of drug. This region is also reported as a potential site for nose-brain transport of drugs.

Barriers To Nasal Absorption[6]

1) Low bioavailability Lipophilic drugs are generally well absorbed from the nasal cavity compared to polar drugs. The pharmacokinetic profiles of lipophilic drugs are often identical to those obtained after an intraven-ous injection and bioavailability approaching

2) Enzymatic Degradation The presence of enzymes in the nasal cavity can form an enzyme barrier that is known to affect the stability of the drug in the nasal cavity. Proteins and peptides are prone to degradation by proteases and amino-peptidase within the nasal cavity. Although it is not exact as the first-pass effect that drugs undergo following oral administration, the enzymatic activity in the nasal cavity can result in decreased therapeutic effects. The presence of P450 enzymes are much higher in the nasal mucosa when compared to the respiratory mucosa.

3) Low membrane transport Another importance fac-tor is low membrane transport is the general rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechan-ism. This is especially the case for drugs that are not easily absorbed across the nasal membrane. It has been shown that for both liquid and powder formula-tions, that are not mucoadhesive, the half life of clear-ance is in the order of 15–20 min.

Factors Influencing Nasal Drug Absorption[7]

1) Physiochemical properties of drug: - Molecular size. Lipophilic-hydrophilic balance. Enzymatic degradation in nasal cavity.

2) Nasal Effect Membrane permeability:- Environmental pH Mucociliary clearance Cold, rhinitis.

3) Delivery Effect Formulation (Concentration, pH, osmolarity) Delivery effects Drugs distribution and deposition. Viscosit

1) Physiochemical properties of drug

Molecular size The molecular size of the drug influence absorption of the drug through the nasal route. The lipophilic drugs have direct relationship between the MW and drug permeation.

Lipophilic-hydrophilic balance[8]
By increasing lipophilicity, the permeation of the compound normally in-creases through nasal mucosa.

Enzymatic degradation In nasal cavity In case of peptides and proteins are having low bio-availability across the nasal cavity, so these drugs may have possibility to undergo enzymatic degradation of the drug molecule in the lumen of the nasal cavity or during passage through the epithelial barrier.

2) Nasal effect factors
Membrane permeability
Nasal membrane permeability is the most important factor, which affect the absorption of the drug through the nasal route. The water soluble drugs and particu-larly large molecular weight drugs like peptides and proteins are having the low membrane permeability.

Environmental pH
The environmental pH plays an important role in the efficiency of nasal drug absorption. Small water-soluble compounds such as benzoic acid, salicylic acid, and alkaloid acid show that their nasal absorption in rat occurred to the greatest extent at those pH values where these compounds are in the nonionised form. However, at pH values where these compounds are partially ionized, substantial absorption was found. This means that the nonionised lipophilic form crosses the nasal epithelial barrier via transcellular route, whe-reas the more lipophilic ionized form passes through the aqueous paracellular route.

Mucociliary Clearance
Mucociliary clearance is a one of the functions of the upper respiratory tract is to prevent noxious substances (allergens, bacteria, viruses, toxins etc.) from reaching the lungs. When such materials adhere to, or dissolve in, the mucus lining of the nasal cavity, they are transported towards the nasopharynx for eventual discharge into the gastrointestinal tract.

Cold, Rhinitis
Rhinitis is a most frequently associated common disease, it influence the bioavailability of the drug. It is mainly classified into allergic rhinitis and common, the symptoms are hyper secretion, itching and sneezing mainly caused by the viruses, bacteria or irritants.

Drugs distribution and deposition
The drug distribution in the nasal cavity is one of the important factors, which affect the efficiency of nasal absorption. The mode of drug administration could effect the distribution of drug in nasal cavity, which in turn will determine the absorption efficiency of a drug. The absorption and bioavailability of the nasal dosage forms mainly depends on the site of disposition. The anterior portion of the nose provides a prolonged nasal residential time for disposition of formulation.

3) Delivery effect factors
Formulation (Concentration, pH, Osmolarity)[9]
The pH of the formulation and nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 because lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the tissue is susceptible to microbial infection. In addition to avoiding irritation, it results in obtaining effi-cient drug permeation and prevents the growth of bac-teria.

Concentration gradient plays very important role in the absorption / permeation process of drug through the nasal membrane due to nasal mucosal damage. Examples for this are nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. Another is absorption of salicylic acid wasfound to decline with concentration. This decline is likely due to nasal mucosa damage by the permanent.

The osmolarity of the dosage form affects the nasal absorption of the drug; it was studied in the rats by using model drug. The sodium chloride concentration of the formulation affects the nasal absorption. The maximum absorption was achieved by 0.462 M sodium chloride concentration; the higher concentration not only causes increased bioavailability but also leads to the toxicity to the nasal epithelium.

Drugs distribution and deposition[10]
The drug distribution in the nasal cavity is one of the important factors, which affect the efficiency of nasal absorption. The mode of drug administration could effect the distribution of drug in nasal cavity, which in turn will determine the absorption efficiency of a drug. The absorption and bioavailability of the nasal dosage forms mainly depends on the site of disposition. The anterior portion of the nose provides a prolonged nasal residential time for disposition of formulation, it enhances the absorption of the drug. And the posterior chamber of nasal cavity will use for the deposition of dosage form; it is eliminated by the mucociliary clearance process and hence shows low bioavailability (Gizurarson S et al., 1991). The site of disposition and distribution of the dosage forms are mainly depends on delivery device, mode of administration, physicochemical properties of drug molecule.

Viscosity[11]
A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drug.

Recommendations to Overcome Barriers to Drug Transport from Nose to Brain

Mucoadhesive polymers, absorption enhancers, and drug delivery devices aimed for precise delivery of drug within the nasal cavity.

There have been a number of novel approaches evaluated in animal models to overcome the barriers to nose-tobrain delivery of drugs via the nasal route. The efforts have been concentrated toward increasing the residence time in the nasal mucosa and modifying the physicochemical properties of the drug using functional excipients and innovative drug delivery technologies.

Prodrug Approach

As previously discussed, the physicochemical properties of drugs, such as the molecular weight and lipophilicity, are critical parameters that have the most influence on drug delivery to the brain via the nasal epithelium. A prodrug strategy can help in modifying these properties in such a manner that the rate and extent of drug absorption increases in the nasal cavity. Experimental studies both in vivo and ex vivo have shown that rapid and complete absorption of drug can be attributed to the degree of lipophilicity and smaller molecular weight of the test compound. Several water-soluble alkyl ester prodrugs of Ldopa were administered to rats via the nasal route, and it was observed that the concentration of butyl ester prodrug of Ldopa was significantly higher in the CNS of rats as compared to parent drug. While this approach has proven to work in many small molecules, this strategy presents some challenges for large molecules, such as proteins and other biologics. It has been difficult to increase the lipophilicity of proteins as there can be significant impact on the spatial structure of the protein, resulting in diminished biological activity.

Innovative Formulation Approach

Maintaining high drug concentration for passive diffusion on the nasal epithelium is important, and in order to achieve this, precise drug deposition and extended residence time must be optimized. There are several nasal formulations and devices that are designed to overcome these challenges. Experimental design in which N-cyclopentyladenosine (CPA) was formulated with mannitol-lecithin and chitosan hydrochloride microparticles were administered to rats via nasal administration showed higher amount of CPA present in the CNS of rats compared to the free CPA. The chitosan hydrochloride formation resulted in a 10-fold higher amount of CPA in the CSF compared to the mannitollecithin microparticles formulation.

Absorption Enhancers & Enzyme Inhibitors

Drugs that are highly lipophilic in nature and also have a very low molecular weight might not need a specialized formulation approach, including use of absorption enhancers. Absorption enhancers can be used in cases where the drug exhibits poor membrane permeability, has large molecular size, and is susceptible to enzymatic degradation by aminopeptides.[17,19,20] Drugs that are formulated using absorption enhancers may impart the following properties that will result in increased drug bioavailability following nasal administration.

– Improve the solubility of the drug.
– Reduce the surface tension of the mucus.
– Decrease the enzyme activity which may keep the drug in its stable form.

Nasal Drug Delivery Devices[12,13]

Drug delivery devices have been found to play an important role in ensuring that the entire drug is delivered to the target site in the nasal cavity. It is difficult to precisely deliver the drug to the olfactory region of the human nasal cavity as this region is found high up in the nasal cavity, above the superior conchae. This area is exposed to a very low volume of the air that penetrates the nasal cavity and can result in lower doses of the drug reaching the olfactory region. Some of the novel proprietary devices that have shown significant differences following administering the drug via the nasal route are shown in table.

Although the initial proof-of-concept studies using these novel nasal drug delivery devices does show promising results, they still need to be further tested using different types of molecules intended to be delivered to the CNS/brain via the nasal cavity/route of drug administration.

Olfactory pathway[14]

Therapeutic modalities once administered via nose, it travels to the olfactory mucosa (also known as olfactory epithelium) represented in the. Olfactory mucosa contains olfactory receptorneurons that are responsible for the transduction. Transduction happens in olfactory receptors on the cilia which is the end of the olfactory receptor neurons. Molecules reach the olfactory receptor neurons by paracellullar or transcellular mechanism. The integrity of nasal epithelium, along with the tight junctions, desmosomes, adherent junctions and space between the epithelial cells allows the entry ofby paracellular transport [The neuronal pathway considered to be determining step of the nose to brain route. Drug moieties travels along axon and via nerve bundle cross the cribriform plate and reach the olfactory bulb which is actually appear on the surface of the brain. From the olfactory nerves, the therapeutic moiety can enter the cerebrospinalfluid (CSF) and olfactory bulb Thedrugcanbedistributed from the CSF to brain by mixing with interstitialfluid in the brain. After a nasal administration of drug it takes only few minutes to reach brain via olfactory transport. Intraneuronal pathway and extraneuronal pathway are the two different pathways of the olfactory neuronal pathway into the brain. Intra-neuronal pathway involves axonal transport and itrequires hours to days for active moiety to reach different regions of the brain. Incase of extra-neuronal pathway which involves transport through perineural channels; it takes only few minutes to reach active

moiety directly to brain The olfactory neuronal pathway innervate to the deeper areas of brain such as cortex, cerebrum and cerebellum. Trigeminal.

Trigeminal Pathway[15]

Trigeminal nerve pathway connecting to the tail part of the brain such as spinal cord, the medulla and the pons. Drug transported through nose via trigeminal nerve pathway by intracellular transport (axonal transport) or by endocytosis. The trigeminal nerve is the largest and fifth cranial nerve andit composed of three branches such as ophthalmic, maxillary and mandibular. Out of these three mainly ophthalmic and maxillary branches plays an important role in nose to brain drug delivery, the neurons from these branches pass direct y through the nasal mucosa. Some segment of trigeminal nerve also ends in the olfactory bulbs Branches from the ophthalmic part of the trigeminal nerve innervate to the dorsalpart of the nasal mucosa and the anterior nose but considering maxillary branch innervate to the turbinates of thenasal mucosa. Once the compounds diffuse through the mucosa of the nasal cavity, it reaches the branches of trigeminal nerves in olfactory and respiratory regions, and via brain stem transported to the axonal route. A part of the trigeminal nerve that passes through the cribriform plate thatmay also involved in the delivery of therapeutics from nasalcavity to the forebrain\. Thorne et al.[21] reported afteran intranasal administration of insulin-like growth factor-I (IGF-I) rapidly reached brain via trigeminal neuronal pathway. Intranasally administered drug/nanoparticles absorbed fromnasal cavity is passage through the mucus, this is the firststep involved in absorption. After passing through the mucus, there are several mechanisms involved in the transportationthrough mucosa. There are paracellullar, transcellular, carriermediated transport, receptormediated transport and transcytosis. Paracellular route is the transport of molecules between the cells. Transcellular route refers to the transport of drugacross the cells this may occur by carrier-mediated transportor by endocytosis. In transcellular route, adsorptive transcytosismechanism involves transport of macromolecules. Thisprocess involves interaction between the ligand in bloodstream and cell surface. This type of interaction may be dueto electrostatic interaction between the positively chargedlig and such as protein or macromolecules and negativelycharged membrane. Nanoparticles and some compoundsundergo transcytosis for the permeation. Kimura et al suggested that mechanism of carriermediatedabsorption takes place by the organic cationtransporters, P-glycoprotein, aminoacid transporters, dopaminetransporter acts as a carrier of molecules in nasal mucosa.

4. Formulation Strategies for Nose to Brain Drug Delivery System[16]

Prodrug approach

In Prodrug approach, the drugs that administered in the form of solution undergo dissolution prior to absorption. Lipophilic drugs get easily absorbed through nasal membrane, However they are poorly water soluble drugs. So the Prodrug approach may be utilized to get of higher hydrophilic character that can made as aqueous formulation of hydrophobic drugs. It should be also focused, when that formulation reaches to systemic circulation, Prodrug must be converted to the parent drug molecule.

Enzymatic inhibitors

Nasal mucus layer and nasal mucosa is act as enzymatic barriers for nasal drug delivery system (they have a wide variety of enzymes). Several approaches was used to avoid the enzymatic degradation, including the use of protease and peptidases inhibitors. Bestatin and comostate amylose were used as aminopeptidases inhibitor and leupeptine, Aprotinin as tyrosine inhibitors is probably involved in the degradation of calcitonin.

Co-solvent

This approach is used to increases the solubility of the drugs. Mostly used co-solvent includes glycerol, ethanol, propylene glycol and ethylene glycol, since these are nontoxic, non-irritant to nasal mucosa and pharmaceutical acceptable.

Absorption enhancer

Absorption enhancer, in which the poor permeability of hydrophilic drugs may be overcome by the used of absorption enhancers that induces reversible modification of epithelial barrier. The absorption enhancer is used in nasal delivery were surfactant (SLS, Poloxamer, tweens, spans), bile salts.

Colloidal Carriers in Nose to Brain Drug Delivery Systems[17]

Colloidal drug carriers include microemulsion, nanoemulsion, nanoparticle, polymeric micelles, liposomes, mucoadhesive solutions and microspheres. The intent behind use of colloidal drug carriers for nose to brain drug delivery was to increases the specifically towards cell or tissue to increases bioavailability of drugs by increasing their diffusion through the biological membranes and protect against enzymatic degradations.

Microemulsion

Microemulsion is a clear, stable, isotropic mixture of oil, water and surfactant are frequently in the combination with co-surfactants these approach is interested to the pharmaceutical scientist because of their considerable potential to act as drug delivery vehicle by incorporating of wide range drug molecules. They offer the advantages of spontaneous formation, easy manufacturing and scale up, thermodynamic stability and it's important to improve the solubilization and bioavailability. Preparing a pharmaceutically acceptable dosage from demands a clear understanding of the microemulsion structure, phase behaviour, factor leading to its thermodynamic stability, factors associated drug release from the formulation and potential uses and limitation of microemulsion system.

Nanoemulsion
Nanoemulsion is an isotropic mixture of oil, surfactant: cosurfactant (Smix) and drug is known as nanoemulsion. The colloidal size ranges from 50-100 nm are often referred to as Miniemulsion, nanoemulsion, ultrafine emulsion or the multiple emulsions. These nanoemulsion appear transparent and translucent to the necked eyes and the possess stability against sedimentation or creaming. These properties make nanoemulsion as carriers of vast interest for fundamental studies and practical applications in various fields like chemical, cosmetic and pharmaceutical and Biopharmaceutical fields.

Polymeric micelles[18]
Polymeric micelles that may serve as nanoscopic drug carriers. Polymeric micelles are the self-assemblies of block of co-polymers and promising nanocarriers for drug and gene delivery, for drug delivery, polymeric micelles have been prepared from biodegradable and biocompatible blocks of copolymers. Polymeric micelles are characterized by core shell structure have reported that mixed micelles of bile salts and fatty acid have a synergistic effect on the nasal absorption of peptides.

Nanoparticles
Nanoparticle is a nanosized particle range size range of 1-1000 nm. It is applicable to improve the solubility of poorly soluble drugs and permeability of drug molecules This nanoparticulate system is based on biodegradable polymers, have been extensive exploited in targeting drug delivery as they offer excellent improvement in nose to brain delivery by protecting the encapsulated drug from biological and chemical degradation, the extracellular transport by P-gp efflux system is increases the CNS availability of drugs. The poly-lactic acid (PLA), poly-glycolic acid (PGA), poly-lactide-co-glycolic acid (PLGA), poly-g-caprolactone (PCL), polymethyl methacrylate, are the polymers known to be biodegradable, biocompatible and non-toxicIllum et al. demonstrated that chitosan based nanoparticles can enhance nose-to-brain delivery of drugs compared to equivalent drug solutions formulations due to the protection of the drug from degradation and/or efflux back into the nasal cavity. Have reported olanzapineloaded PLGA nanoparticles for the treatment of psychotic illness, schizophrenia, via nose to brain drug delivery platform.

Nasal Delivery Devices[19]
Nasal drug delivery devices is versatile tool for direct drug delivery in nasal cavity by using various nasal device devices do exist, and more are in development.

Powder formulation devices
The powder nasal devices are more convenient and it is having a maximum stability than liquid nasal devices. In powder nasal devices preservatives are not required for preparation. It is having a larger dose of drug and they improve stability of formulation. They can be free from microbial growth. The nasal powder administration is increases the patient compliances and patient acceptance.

Insufflators[20]
In this nasal devices, to deliver the pharmaceutical molecule for inhalation. This devices is mainly constructed in the straw or tubes which contains the pharmaceutical molecules. It is a pre-dose powder capsules.

Dry powder inhaler[21]
Dry powder inhalers (DPIs)) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales. These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus. The dose that can be delivered is typically less than a few tens of milligrams in a single breath since larger powder doses may lead to provocation of cough Pressurized Metered Dose Inhale (PMDI).

The pressurized metered dose inhaler is a nasal device (Fig.7) to deliver optimum amount of drug to the lungs, this is a short burst aerosolized drug that inhaled the patient. A PMDI devices are important to deliver the optimum amount of medication to the lungs.

Classification of Polymers[22, 23, 24]
Hydrophilic Polymers These are the water-soluble polymers that swell indefinitely in contact with water and eventually undergo complete dissolution, *e.g.* Methylcellulose, hy- droxyethyl cellulose, hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose, carbomers, chitosan and plant gums *etc.*

Hydrogels These are water swellable materials, usually a cross-link polymer with limited swelling capacity, *e.g.* poly(acrylic acid co acrylamide) copolymers, carrageenan, sodium alginate, guar gum and modified guar gum *etc.*

Thermoplastic Polymers[25,26]
These polymers include the non-erodible neutral polystyrene and semi crystalline bio- erodible polymers, which generate the carboxylic acid groups as they degrade, *e.g.* polyanhydrides and polylactic acid. Various synthetic polymers used in mucoadhesive formulations include polyvinyl alcohol, polyamides, polycarbonates, polyalkylene glycols, polyvinyl ethers, esters and halides, polymethacrylic acid, polymethylmethacrylic acid, methyl- cellulose, hydroxypropyl cellulose, hydroxypropyl methylcel- lulose and sodium carboxymethylcellulose.

Various biocompatible polymers used in mucoadhesive formulations include cellulose-based polymers, ethylene glycol polymers and its copolymers, oxyethylene polymers, polyvinyl alcohol, polyvinyl acetate and esters of haluronic acid.Various biodegradable polymers used in mucoadhesive formulations are poly(lactides), poly(glycolides), poly(lac- tide-co-glycolides), polycaprolactones, and polyalkyl cyanoacrylates. Polyorthoesters, polyphosphoesters, polyanhydrides, polyphosphazenes are the recent additions to the polymers.

Mucoadhesive Microspheres[25,26,27]

Mucoadhesive microspheres include microparticles and microcapsules (having a core of the drug) of 1—1000 *mm* in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it, respectively. Microspheres, in general, have the potential to be used for targeted and controlled release drug delivery; but coupling of mucoadhesive properties to microspheres has additional advantages, *e.g.* 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, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, *etc.* on the surface of the microspheres.

Mucoadhesive microspheres 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. Application of mucoadhesive microspheres to the mu- cosal tissues of ocular cavity, gastric and colonic epithelium is used for administration of drugs for localized action. Prolonged release of drugs and a reduction in frequency of drug administration to the ocular cavity can highly improve the patient compliance. The latter advantage can also be obtained for drugs administered intra-nasally due to the reduction in mucociliary clearance of drugs adhering to nasal mucosa. Microspheres prepared with mucoadhesive and bioerodable polymers undergo selective uptake by the M cells of Peyer patches in gastrointestinal (GI) mucosa. This uptake mechanism has been used for the delivery of protein and peptide drugs, antigens for vaccination and plasmid DNA for gene therapy. Moreover, by keeping the drugs in close proximity to their absorption window in the GI mucosa. The mu- coadhesive microspheres improve the absorption and oral bioavailability of drugs like furosemide and riboflavin. The concept of a non-invasive single shot vaccine, by means of mucosal immunization, offers controlled release of antigens and thus forms another exquisite application of mucoadhesive microspheres.

Preparation of Mucoadhesive Microspheres[28]

Mucoadhesive microspheres can be prepared using any of the following techniques.

Solvent Evaporation

It is the most extensively used method of microencapsulation, first described by Ogawa *et al.* A buffered or plain aqueous solution of the drug (may contain a viscosity building or stabilizing agent) is added to an organic phase consisting of the polymer solution in solvents like dichloromethane (or ethyl acetate or chloroform) with vigorous stirring to form the primary water in oil emulsion. This emulsion is then added to a large volume of water containing an emulsifier like PVA or PVP to form the multiple emulsion (w/o/w). The double emulsion, so formed, is then subjected to stirring until most of the organic solvent evaporates, leaving solid microspheres. The microspheres can then be washed, centrifuged and lyophilize to obtain the free flowing and dried microspheres.

Hot Melt Microencapsulation[29]

This method was first used by Mathiowitz and Langer to prepare microspheres of polyanhydride copolymer of poly[bis(p-carboxy phenoxy) propane anhydride] with sebacic acid. In this method, the polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 mm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5° 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 mm 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.

Solvent Removal[30]

It is a non-aqueous method of microencapsulation, particularly suitable for water labile polymers such as the ploy anhydrides. In this method, drug is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride. This mixture is then suspended in silicone oil containing span 85 and methylene chloride. After pouring the polymer solution into silicone oil, petroleum ether is added and stirred until solvent is extracted into the oil solution. The resulting microspheres can then be dried in vacuum.

Hydrogel Microspheres[31]

Microspheres made of gel-type polymers, such as alginate, are produced by dissolving the polymer in an aqueous solution, suspending the active ingredient in the mixture and extruding through a precision device, producing micro droplets which fall into a hardening bath that is slowly stirred. The hardening bath usually contains calcium chloride solution, whereby the divalent calcium ions crosslink the polymer forming gelled microspheres. The method involves an "all-aqueous"

system and avoids residual solvents in microspheres. Lim and Moss developed this method for encapsulation of live cells, as it does not involve harsh conditions, which could kill the cells. The surface of these microspheres can be further modified by coating them with polycationic polymers, like polylysine after fabrication. The particle size of microspheres can be controlled by using various size extruders or by varying the polymer solution flow rates.

Spray Drying[32]

In this process, the drug may be dissolved or dispersed in the polymer solution and spray dried. The quality of spray-dried microspheres can be improved by the addition of plasticizers, *e.g.* citric acid, which promote polymer coalescence on the drug particles and hence promote the formation of spherical and smooth surfaced microspheres. The size of microspheres can be controlled by the rate of spraying, the feed rate of polymer drug solution, nozzle size, and the drying temperature. This method of microencapsulation is particularly less dependent on the solubility characteristics of the drug and polymer and is simple, reproducible, and easy to scale up.

Phase Inversion Microencapsulation[33]

The process involves addition of drug to a dilute solution of the polymer (usually 1—5%, w/v in methylene chloride). The mixture is poured into an unstirred bath of strong non-solvent (petroleum ether) in a solvent to non-solvent ratio of 1: 100, resulting in the spontaneous production of microspheres in the size range of 0.5—5.0 *mm* can then be filtered, washed with petroleum ether and dried with air. This simple and fast process of microencapsulation involves relatively little loss of polymer and drug.

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