

**“OVERVIEW ON INTRANASAL MUCOADHESIVE DRUG DELIVERY”****Snehal S. Badadare\*, Raje V. N. and Jadhav R. S.**

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**\*Corresponding Author****Snehal S. Badadare**GES College of Pharmacy  
(D. Pharm.) Limb, Satara.**ABSTRACT**

Designing mucoadhesive drug delivery system is a novel approach in nasal drug delivery, which enhances the nasal residential time of the drug molecule and hence enhances the absorption and bioavailability of nasally administered drug products. Bioadhesion is the ability of natural material to adhere to a biological tissue or membrane for a prolonged period of time. Mucoadhesive system is the ideal choice of drug delivery system for systemic nasal drug delivery because it improves the nasal residential time. Intimate contact of drug delivery system to the nasal mucosa not only prolongs the duration of action but also increases extent of absorption.

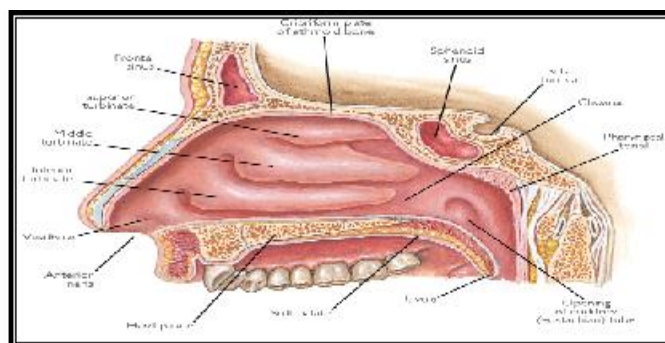
**KEYWORDS:** Mucoadhesive, Nasal Drug Delivery, Microparticles.**INTRODUCTION**

The most desirable and convenient method of drug administration is the oral route because of their ease of administration. However, in many instances oral administration is not desirable when the drug undergoes significant degradation via first pass effect in liver. Hence, lack of systemic absorption through the gastrointestinal tract led to research on alternate routes of drug delivery such as parenteral, intramuscular, subcutaneous, intranasal, transdermal, etc.<sup>[1,2]</sup> Intranasal (IN) administration is a needle free and hence an ideal alternative to the parenteral route for systemic drug delivery. Nasal mucosa consists of a rich vasculature and a highly permeable structure for systemic absorption. Drug administration through the nasal cavity is easy and convenient. Avoidance of first pass metabolism is the main advantage of nasal route of drug delivery.<sup>[1,3]</sup>

Possible pathways for a drug to permeate across the nasal mucosa are passive transportation carriers mediated, transcytosis and transport through tight junctions. Nasal application of drugs is suggested to be the most viable alternative to the parenteral administration.<sup>[4]</sup>

Nasal drug delivery system provides excess of easy application of drug, with the possibility of self administration by removing the chance of unwanted painful condition associated with injection form of drug delivery. Furthermore, lipophilic and low molecular weight drugs can easily penetrate through nasal mucosa with less degradation. Fast absorption can be achieved due to large absorption surface area and high vascularisation. Nasal route can be used as an alternative to parenteral in case of emergency therapy. Nasal drug delivery system is a potential route for direct delivery of drug to the central nervous system through olfactory region by bypassing hepatic first pass metabolism.

### 1.1 ANATOMY AND PHYSIOLOGY OF NASAL CAVITY



**Figure 1: Anatomy of Nasal Cavity.**

In studying drug absorption from the nasal mucous membrane, it is essential to have a clear understanding of anatomy and physiology of the nose, and how it relates to the characteristics of the delivery system used. The nasal passage which runs from the nasal vestibule to the nasopharynx has a depth of approximately 12-14 cm. In this passage, the nasal cellular apparatus is in close contact with mucus which protects the mucosa from the inspired air. There are 3 distinct functional zones in the nasal cavities, viz. vestibular, respiratory and olfactory regions. The vestibular area serves as a baffle system and its surface is covered by a common pseudo stratified epithelium where the long hairs may provide the function of filtering air borne particles. Respiratory area has a surface lined by a pseudo stratified columnar epithelium and is normally covered by a dense layer of mucus that is constantly moving towards the posterior apertures of the nasal cavity by a powerful system of motile

cilia. The olfactory segment is lined with a specialized type of pseudo stratified columnar epithelium, known as olfactory epithelium, which contains receptors for the sense of the smell. This segment is located along the dorsal roof of the nasal cavity. Olfactory mucosal cell types include: bipolar neurons, supporting (sustentacular) cells, basal cells, and Bowman's glands. The total surface area of both nasal cavities is about 150 cm<sup>2</sup> and the total volume is about 15 ml. Approximately 1.5 cm from the nostrils is the narrowest portion of the entire airway, the internal ostium (nasal valve), with a cross-sectional area of about 30 mm<sup>2</sup> on each side. The nasal valve accounts for approximately 50% of the total resistance to respiratory airflow from the nostril to the alveoli. Each of the two nasal cavities is limited by the septal wall and the lateral wall, dominated by inferior, middle and superior turbinates (Figure 1).<sup>[8]</sup> They are important for maintaining the slit-like cavity, thus facilitating humidification and temperature regulation of inspired air. Under and lateral to each of the turbinates are passages called the inferior, middle (and superior) meatus. The individually variable caliber and shape of the lumen of the nasal cavities make it difficult to give uniform recommendations for intranasal drug administration.<sup>[5,6,7,8]</sup>

### **Blood Supply to Nasal Cavity**

Blood supply comes from branches of both the internal and external carotid artery, including branches of the facial artery and maxillary artery. The named arteries of the nose are

- **Sphenopalatine Artery**, a branch of maxillary artery.
- **Anterior Ethmoidal Artery**, a branch of ophthalmic artery.
- Branches of the **facial artery** supplying the vestibule of the nasal cavity.<sup>[7]</sup>

At least 50% of the blood flow in the nasal mucosa is normally shunted through arteriovenous anastomoses.<sup>[6,7]</sup>

### **Mucus Secretion and Mucociliary Clearance<sup>[9,10]</sup>**

The submucosal glands, which secrete the greater quantity of nasal mucus, comprise both mucus cells, secreting the mucus gels, and serous cells, producing a watery fluid. Mucus is also released from the goblet cells as mucus granules. Mucus secretion is a complex mixture of many substances and consists of about 95% water, 2% mucin, 1% salts, 1% of other proteins such as albumin, immunoglobulins, lysozyme and lactoferrin, and <1% lipids. About 1.5–2 litre of nasal mucus is produced daily. Maintaining optimal MCC is very important in order to prevent respiratory tract infections. The MCC can be influenced by environmental

and pathological conditions. These factors ultimately alter nasal drug delivery and the performance of nasal mucoadhesive formulations, and should be taken into account during product development.<sup>[9,10]</sup>

### **Nasal Enzymes**

Many enzymes exist in nasal secretions. These are cytochrome P-450 dependent monooxygenases, lactate-dehydrogenases, oxidoreductases, hydrolases, acid phosphatase, esterase, NAD<sup>+</sup> - dependent formaldehyde dehydrogenase, leucine amino-peptidase, lysosome proteinases and their inhibitors.

### **Nose to Brain Delivery**

There are two mechanisms underlying the direct nose to brain drug delivery, one is intracellular transport mediated route and two extracellular transport mediated routes. The intracellular transport mediated route is a relatively slow process, taking hours for intranasally administered substances to reach the olfactory bulb. The two extracellular transport mediated routes could underlie the rapid entrance of drug into the brain which can occur within minutes of intranasal drug administration. In the first extracellular transport based route intranasally administered substances could first cross the gap between the olfactory neurons in the olfactory epithelium which are subsequently transported in to the olfactory bulb. In the second extracellular transport based route, intranasal administered substances may be transported along trigeminal nerve to bypass BBB. After reaching the olfactory bulb of trigeminal region the substances may enter in to other regions of brain by diffusion, which may also be facilitated by perivascular pump that is driven by arterial pulsation. Delivery of drugs to the central nervous system (CNS) remains a challenge in the development of therapeutic agents for central targets due to the impenetrable nature of the drug through blood-brain barrier (BBB). The BBB obstruct the substrate penetration based on several characteristics, including lipophilicity, molecular size and specificity for a variety of ATP-dependent transport systems.<sup>[9]</sup>

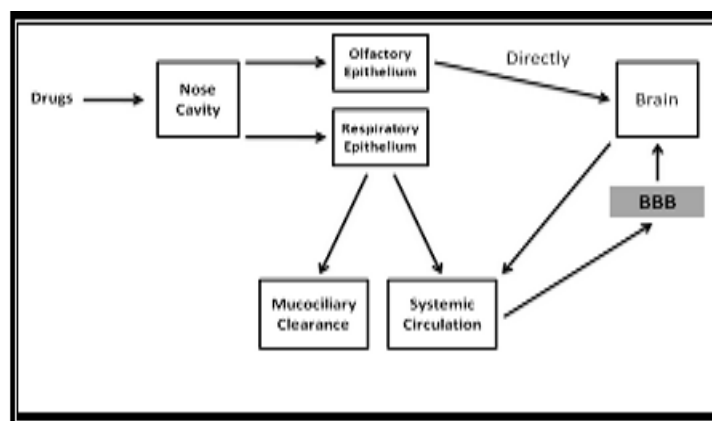


Figure 2: Nose to brain transport routes.

## 1.2 NASAL DRUG DELIVERY

Intranasal (IN) delivery is suitable for the local and systemic delivery of diverse therapeutic compounds. Among the non-invasive routes, nasal administration offers promising potential as a viable alternative for the delivery of some drugs. Hence there has been a surge of interest that has led to many investigations involving the nasal cavity as a feasible site for the administration of much therapeutic agents. Nasal drug delivery offers many advantages as below. However, it also possesses few limitations which are also mentioned below.

### Advantages and limitations of Nasal Drug Delivery

#### ADVANTAGES<sup>[11,12]</sup>

- Avoids degradation of drug in gastrointestinal tract resulting from acidic or enzymatic degradation.
- Avoids degradation of drug resulting from hepatic first pass metabolism.
- Results in rapid absorption and onset of effect.
- Results in higher bioavailability thus use lower doses of drug & lower risk of overdose.
- Easily accessible, non-invasive route & Self medication is possible through this route.
- Direct transport into systemic circulation and CNS is possible.
- Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.
- By pass the BBB (Blood Brain Barrier), hepatic first pass metabolism is avoided.
- Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.

**Limitations**<sup>[11,12]</sup>

- Volume that can be delivered into nasal cavity is restricted to 25–200 µl
- High molecular weight compounds cannot be delivered through this route.
- Adversely affected by pathological conditions.
- Normal defense mechanisms like mucociliary clearance and ciliary beating affects the permeability of drug.
- Enzymatic barrier to permeability of drugs.
- Irritation of nasal mucosa by drugs.
- 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.
- Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.

Another limitation of nasal drug delivery includes rapid mucociliary clearance of the therapeutic agent from the site of deposition resulting in a short span of time available for absorption. However, it can be overcome by using bioadhesive polymers that increase residence time of the formulation in the nasal cavity thereby improving absorption.

**Mechanism for Drug Permeation**

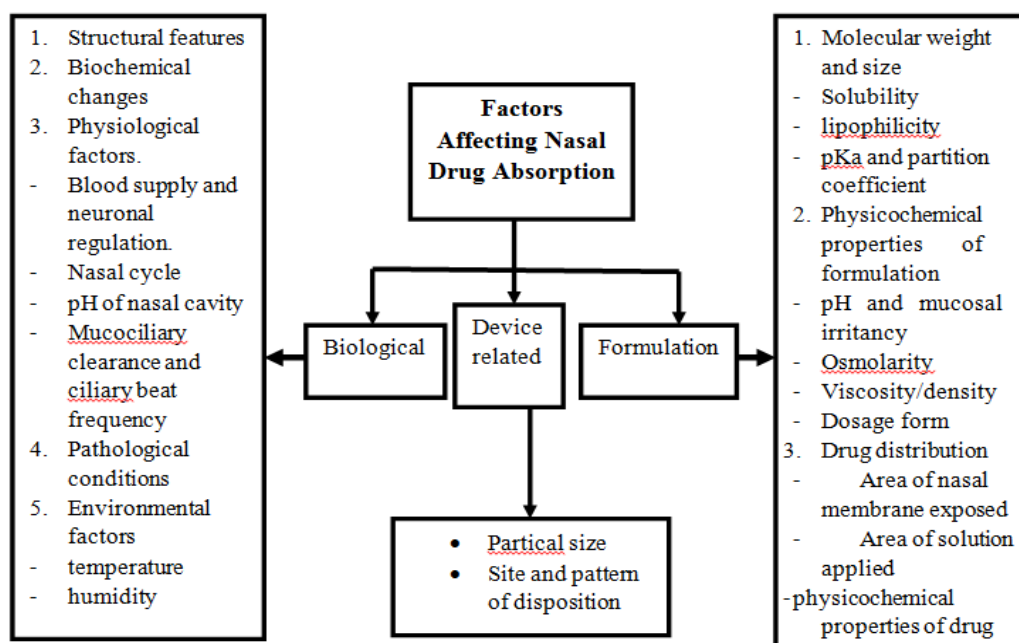
There are several mechanisms for absorption through the mucosa. These include transcellular or Simple diffusion across the membrane, paracellular transport *via* movement between cell and transcytosis by vesicle carriers. Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and limited residence time in the cavity. Several mechanisms have been proposed but the following two mechanisms have been considered predominantly.<sup>[13,11,14,8,15]</sup>

- The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. This route is slow and passive. There is an inverse log log correlation between intranasal absorption and the molecular weight of water soluble compounds. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons.
- The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity.

- Drugs also cross cell membranes by an active transport route *via* carrier-mediated means or transport through the opening of tight junctions.

### 1.3 Factors Affecting Nasal Drug Absorption

The factors affecting permeability of drug through the nasal mucosa can broadly be classified into three categories as shown in following diagram.<sup>[16]</sup>



**Figure 3: Variable factors affecting the permeability of drugs through the nasal mucosa.**

### Strategies to Improve Bioavailability

A wide number of formulation strategies are made available to improve the bioavailability of nasal dosage forms. The basic underlying mechanisms for bioavailability enhancement are described in the following table. Any one of the approaches or combination of two or more strategies is widely used to improve the bioavailability of nasal formulations.<sup>[17]</sup>

**Table No. 1: Strategies to Improve Nasal Bioavailability.**

| Sr. No. | Strategy                         | Examples  |
|---------|----------------------------------|---|
| 1.      | Nasal Enzyme Inhibitors          | Bestatin, Amastatin, Boroleucine, Fusidic Acids And Bile Salts      |
| 2.      | Nasal Permeation Enhancers       | Cyclodextrins, surfactants, saponins, phospholipids                 |
| 3.      | Prodrug Approach                 | Cyclic Prodrugs, Esters, Derivatization of C and N termini          |
| 4.      | Nasal Mucoadhesive Drug Delivery | Carbopol, Polycarbophil, Cellulose Derivatives, Lecithin, Chitosan. |
| 5.      | Particulate Drug Delivery        | Microparticless/Particulate, Nanoparticles, Liposomes               |



#### 1.4 NASAL FORMULATIONS

Designing of nasal formulation depends upon the therapeutic need of the particular drug molecule, duration of action and duration of therapy. Both controlled release and conventional release drug delivery are possible through nasal route. Requirement of the pharmaceutical excipients depend upon the mode of drug delivery, i.e. local or systemic drug delivery.<sup>[11,9,14,8,15]</sup> Wide range of nasal formulations has been studied so far, and these include:

- **Nasal Drops:** Nasal drops are one of the most simple and convenient delivery systems among all formulations. The main disadvantage of this system is the lack of dose precision. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.
- **Nasal Powders:** The advantages of a nasal powder dosage form are the absence of preservative and superior stability of the drug in the formulation. An additional advantage of this system is local application of drug, but nasal mucosa irritancy and metered dose delivery are some of the challenges for formulation scientists and device manufacturers who are interested in powder dosage forms
- **Nasal Sprays:** Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose anywhere from 25 to 200 µl. The particle size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly. Solution and suspension sprays are preferred over powder sprays because powder results in mucosal irritation.
- **Nasal Emulsions, Microemulsions and Nano/Microparticles:** Nasal emulsions offer the advantages for local application mainly due to the viscosity. One of the major disadvantages is poor patient acceptability. The physical stability of emulsion formulations and precise delivery are some of the main formulation issues.
- **Nasal Gels:** Nasal gels are thickened solutions or suspensions, of high-viscosity. Vitamin B12 & Apomorphine gel are successfully used to achieve desired therapeutic concentrations of drug.

#### 1.5 MUCOADHESIVE DRUG DELIVERY SYSTEM

Mucoadhesive drug delivery systems are the systems which utilize the property of mucoadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time.



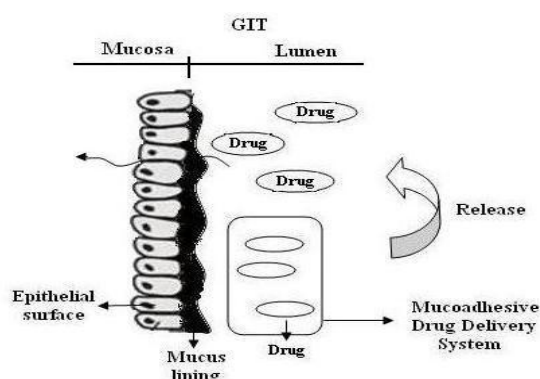
Bioadhesion is an integral phenomenon in which two materials, at least one of which is biological are held together by means of interfacial forces. In the case of polymer attached to mucin layer of a mucosal tissue, the term mucoadhesion is used. The mucosal layer lines a number of regions of the body including the nose, gastrointestinal tract, urogenital tract, the airways, the ear and eye.

### ➤ Mechanism of Mucoadhesion

Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Mucoadhesion has the following mechanism:

1. Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon).
2. Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane
3. Formation of chemical bonds between the entangled chains.

Residence time for most mucosal routes is less than an hour and typically in minutes, it can be increased by the addition of an adhesive agent in the delivery system which is useful to localize the delivery system and increases the contact time at the site of absorption. The exact mechanism of mucoadhesion is not known between the mucoadhesive polymer and mucin occurs which is followed by the interpenetration of polymer and mucin. The adhesion is prolonged due to the formation of Vander Waals forces, hydrogen bonds and electrostatic bonds.<sup>[19]</sup> A general mechanism of mucoadhesion drug delivery system is show in figure no 4.<sup>[18]</sup>



**Figure 4: Mechanism of Mucoadhesion.**

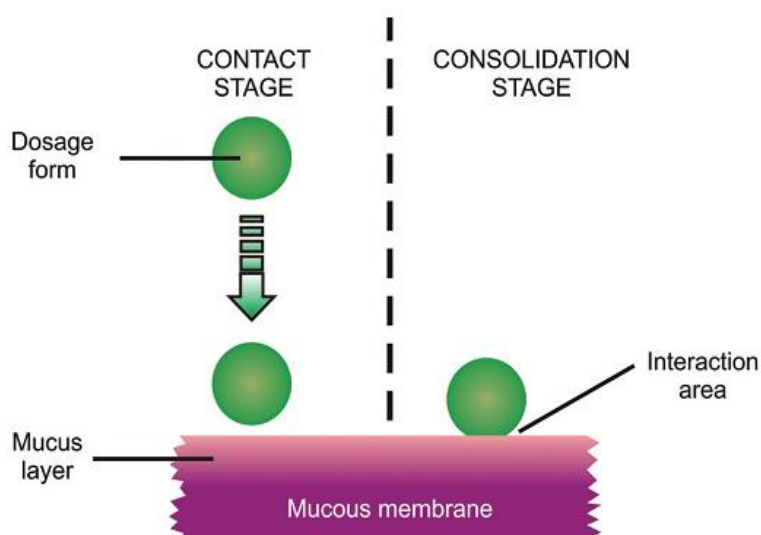
The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion arises and, for a mucoadhesive to be successful, the attraction forces must dominate. Each step can be facilitated by the nature of the dosage form

and how it is administered. For example, a partially hydrated polymer can be adsorbed by the substrate because of the attraction of surface water.

### ➤ Stages of Mucoadhesion

**Contact Stage:** The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer.<sup>[20]</sup>

**Consolidation Stage:** Various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion. In this step, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds.<sup>[20]</sup>



**Figure 5: Two Step of Mucoadhesion Process.**

### ➤ THEORIES OF MUCOADHESION

**Wetting Theory** – The wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. 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.<sup>[21]</sup>

**Diffusion Theory-** According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permeable adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of

contact. The diffusion coefficient in turns depends on the value of the molecular weight between cross linking and decreases significantly as the cross linking density increases.<sup>[21]</sup>

**Electronic Theory**<sup>[21]</sup> – According to this theory, electron transfer occurs upon contact of adhesive polymer with a mucus glycoprotein network because of differences in their electronic structures. This results in the formation of electrical double layer at the interface. 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. Two types of chemical bonds resulting from these forces can be distinguished as primary chemical bonds of covalent nature and secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.<sup>[21]</sup>

**Fracture Theory-** This is perhaps the most-used theory in studies on the mechanical measurement of mucoadhesion. It analyses the force required to separate two surfaces after the adhesion is established. This force,  $\sigma_m$ , is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force,  $F_m$ , and the total surface area,  $A_o$ . Since the fracture theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains, involved in the adhesive interaction.<sup>[19,21]</sup>

$$(\text{eq.}): \sigma_m = F_m/A_o \dots\dots (1)$$

**Cohesive Theory-** The cohesive theory proposes that the phenomena of bioadhesion are mainly due to intermolecular interaction amongst like molecule. Based upon the above 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).<sup>[21]</sup>

**Mechanical Theory-** Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface of a mucoadhesive liquid. Moreover, such roughness

increases the interfacial area available to interactions, thereby aiding dissipating energy and can be considered the most important phenomenon of the process.<sup>[19,20]</sup>

➤ **The Mucoadhesive / Mucosa Interaction:-**

• **Chemical Bonds**

For adhesion to occur, molecules must bond across the interface. These bonding can occur by following way.<sup>[22]</sup>

- a. **Ionic Bonds**- where two oppositely charged ions attract each other via electrostatic interaction form a strong bond (e.g. in a salt crystal).
- b. **Covalent Bonds**- where electrons are shared, in pairs, between the bonded atoms in order to 'fill' the orbitals in both. These are also strong bonds.
- c. **Hydrogen Bonds**- here a hydrogen atom, when covalently bond as oxygen, fluorine or nitrogen, carries a slight positively charge and is therefore is attracted to other electronegative atoms. The hydrogen can therefore be thought of as being shared, and the bond formed is generally weaker than ionic or covalent bonds.
- d. **Van-der-Waals Bonds**- these are some of the weakest forms of interaction that arise from dipole dipole and dipole-induced dipole attractions in polar molecules, and dispersion forces with non- polar substances.
- e. **Hydrophobic Bonds**- more accurately described as the hydrophobic effect, these are indirect bonds (such groups only appear to be attracted to each other) that occur when non present in an aqueous solution. Water molecules adjacent to non-bonded structures, which lower the system entropy. There is therefore an increase in the tendency of non-polar groups to associate with each other to minimize this effect.

## **1.6 POLYMERS USED IN MUCOADHESIVE DRUG DELIVERY SYSTEM**

Polymers are classified into two types<sup>[18,23,24]</sup>

### **1. Synthetic Polymers**

### **2. Natural Polymers**

#### **1. Synthetic polymers are divided into two types.**

##### **a. Non-Biodegradable Polymers**

e.g. Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers.

##### **b. Biodegradable Polymers**

e.g. Lactides, Glycolides & their co polymers, Poly alkyl cyano acrylates, Poly anhydrides.

## 2. Natural Polymers

- **Proteins** : Albumin, Gelatin, and Collagen
- **Carbohydrates** : Agarose, Carrageenan, Chitosan, Starch.
- **Chemically Modified Carbohydrates** : Poly dextran, Poly starch.

In case of non-biodegradable drug carriers, when administered parenterally, the carrier remaining in the body after the drug is completely released poses possibility of carrier toxicity over a long period of time. Biodegradable carriers which degrade in the body to non-toxic degradation products do not pose the problem of carrier toxicity and are more suited for parenteral applications.

### Synthetic Polymers

Poly alkyl cyano acrylates is a potential drug carrier for parenteral as well as other ophthalmic, oral Preparations. Poly lactic acid is a suitable carrier for sustained release of narcotic antagonist, anti cancer agents such as cisplatin, cyclo phosphamide, and doxorubicin. Sustained release preparations for anti malarial drug as well as for many other drugs have been formulated by using of co-polymer of poly lactic acid and poly glycolic acid. Poly anhydride microparticless (40µm) have been investigated to extend the precorneal residence time for ocular delivery. Poly adipic anhydride is used to encapsulate timolol maleate for ocular delivery.

### Natural Polymers

**Albumin** is a widely distributed natural protein. It is considered as a potential carrier of drug or proteins. It is widely used for the targeted drug for the targeted drug delivery to the tumors cells.

**Gelatin** microparticless can be used as efficient carrier system capable of delivering the drug or biological response modifiers such as interferon to phagocytes.

**Starch** belongs to carbohydrate class. It consists of principle glucopyranose unit, which on hydrolysis yields D-glucose. It being a poly saccharide consists of a large number of free OH groups. By means of these free OH groups a large number of active ingredients can be incorporated within as well as active on surface of microparticless.

**Chitosan** is a deacylated product of chitin. The effect of chitosan has been considered because of its charge. It is insoluble at neutral and alkaline pH values, but forms salts with inorganic and organic salts. Upon dissolution, the amino groups of chitosan get protonated, and the resultant polymer becomes positively charged. 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.<sup>[24]</sup>

Chitosan are the most widely used bioadhesive polymers for nasal drug delivery. It has been reported that the clearance half-life was 25% greater for chitosan microparticless than for starch microparticless, this may be due to difference in surface charge, molecular contact, and flexibility of polymers. chitosan exert a transient inhibitory effect on mucocilliary clearance of the bioadhesive formulations.<sup>[25]</sup>

**Hydrophilic Polymers:** The polymers within this category are soluble in water. Matrices developed with these polymers swell when put into an aqueous media with subsequent dissolution of the matrix. The polyelectrolytes extend greater mucoadhesive property when compared with neutral polymers<sup>[14]</sup> Anionic polyelectrolytes, e.g. poly (acrylic acid) and carboxymethyl cellulose have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer.

Chitosan provides an excellent example of cationic polyelectrolyte, which has been extensively used for developing mucoadhesive polymer due to its good biocompatibility and biodegradable properties. “Chitosan undergoes electrostatic interactions with the negatively charged mucin chains there by exhibiting mucoadhesive property”. The ionic polymers may be used to develop ionic complex with the counter-ionic drug molecules so as to have a drug delivery matrix exhibiting mucoadhesive property. Non-ionic polymers, e.g. poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, poly (vinyl alcohol) and poly (vinyl pyrrolidone) have also been used for mucoadhesive properties.<sup>[18,23,21]</sup>

**Hydrogels:** Hydrogels can be defined as three-dimensionally crosslinked polymer chains which have the ability to hold water within its porous structure. The water holding capacity of the hydrogels is mainly due to the presence of hydrophilic functional groups like hydroxyl,

amino and carboxyl groups.<sup>[14]</sup> Hydrogels prepared by the condensation reaction of poly (acrylic acid) and sucrose indicated an increase in the mucoadhesive property with the increase in the crosslinking density and was attributed to increase in the poly (acrylic acid) chain density per unit area. Acrylates have been used to develop mucoadhesive delivery systems which have the ability to deliver peptide bioactive agents to the upper small intestine region without any change in the bioactivity of the peptides. Wheat germ agglutinin helped in improving the intestinal residence time of the delivery system by binding with the specific carbohydrate moieties present in the intestinal mucosa.<sup>[18,23]</sup>

**Thiolated Polymers:** The presence of free thiol groups in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin which can substantially improve the mucoadhesive properties of the polymers e.g. poly (acrylic acid) and chitosan) in addition to the paracellular uptake of the bioactive agents. Various thiolated polymers include chitosan– iminothiolane, poly (acrylic acid)–cysteine, poly (acrylic acid)–homocysteine, chitosan–thioglycolic acid, chitosan–thioethylamidine, alginate–cysteine, poly (methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine.<sup>[23]</sup>

**Lectin-Based Polymers:** Lectins are proteins which have ability to reversibly bind with specific sugar carbohydrate residues and are found in both animal and plant kingdom. The specific affinity of lectins towards sugar or carbohydrate residues provides them with specific cyto-adhesive property and is being explored to develop targeted delivery systems. Various lectins which have shown specific binding to the mucosa include lectins extracted from *Ulex europaeus* I and *Lens culinaris*.<sup>[18,23]</sup> A short list of Mucoadhesive polymers is given in Table no 2.<sup>[18]</sup>

**Table No. 2: List of Natural and Synthetic Polymers.**

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



➤ **Characteristics of Ideal Bioadhesive Polymers**

- It should show bioadhesive properties in both dry and liquid state.
- It should be able to accommodate both oil and water soluble drugs for the purpose of controlled drug delivery.
- It should demonstrate local enzyme inhibition and penetration enhancement properties.
- It should show specificity for attachment to an area or cellular site.
- It should show specificity and stimulate endocytosis.
- It should be inert and compatible with the environment & have a good mechanical strength.
- It should be easy and inexpensive to fabricate.
- It should possess a wide margin of safety both locally and systemically.

### **1.7 MICROPARTICULATE DRUG DELIVERY SYSTEM**

Microparticles are a type of drug delivery systems where the particle size ranges from one micron (1000 nm) to few mm. This microencapsulation technology allows protection of drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities, or masking of unpleasant taste. Hence, they play an important role as drug delivery systems aiming at improved bioavailability of conventional drugs and minimizing side effects.

➤ **ADVANTAGES OF MICROPARTICLES<sup>[31]</sup>**

1. Effective delivery of agents which are insoluble or sparingly soluble in water.
2. They protect the drugs from environment & increased the relative bioavailability of drugs.
3. Taste and odor masking.
4. The formulation of microparticles also provides the method of targeting the drug delivery to specific sites.
5. They provide the sustained release formulation with lower dose of drug to maintain plasma concentration & improved patient compliance.
6. The microparticles hold great potential in reducing the dosage frequency & toxicity of drugs.
7. They also have an advantage of being stored in dry particle or suspension form with little or no loss of activity over an extended storage period.

➤ **DISADVANTAGES**<sup>[32]</sup>

1. Reproducibility is less.
2. Process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
3. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents and
4. The costs of the materials and processing of the controlled release preparation, which may be substantially higher than those of standard formulations.

➤ **MORPHOLOGY OF MICROPARTICLE**

Microencapsulation is a technology used to entrap solids, liquids, or gases inside a polymeric matrix or shell. Microparticles are particulate dispersions or solid particles. Two general micromorphologies of microparticles can be distinguished- microcapsules and microparticles.<sup>[32]</sup>

**a. Microcapsule:** Is a system in which drug containing core is completely surrounded by a polymer shell. The core can be solid, liquid or gas; the shell is a continuous, porous or non-porous polymeric layer. Microcapsules are classified into three basic categories as monocored, polycored and matrix type. Monocored microcapsules have a single hollow chamber within the capsule. Polycore microcapsules have a number of different sized chambers within the shell. Matrix type micro particle has the active ingredients integrated within the matrix of the shell. However, the morphology of the internal structure of a micro particle depends on the shell materials and the micro encapsulation methods that are employed.

**b. Microspheres:** In which the drug substance is either homogeneously dissolved or dispersed in a polymeric matrix. Microspheres show different release properties compared to true microcapsules.

➤ **RELEASE MECHANISM**

Encapsulated material provides controlled, sustained or targeted release of core material. Drug release from the microparticles occurs by following mechanism like Diffusion & Erosion.<sup>[32]</sup>

- a) **Diffusion:** On contact with aqueous fluids, water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.
- b) **Erosion:** Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle. The polymer erosion, i.e. loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as the water penetrates within it leading to the plasticization of the matrix.

## ➤ METHODS OF PREPARATION OF MICROPARTICLES

### 1. Emulsion-Solvent Evaporation

The solvent evaporation method involves the emulsification of an organic solvent (usually methylene chloride) containing dissolved polymer and dissolved/dispersed drug in an excess amount of aqueous continuous phase, with the aid of an agitator. The concentration of the emulsifier present in the aqueous phase affects the particle size and shape. When the desired emulsion droplet size is formed, the stirring rate is reduced and evaporation of the organic solvent is realized under atmospheric or reduced pressure at an appropriate temperature. subsequent evaporation of the dispersed phase solvent yields solid polymeric microparticles entrapping the drug. The solid microparticles are recovered from the suspension by filtration, centrifugation, or lyophilization.<sup>[31]</sup>

### 2. Polymerization techniques

Mainly two techniques are used for the preparation of microparticles are classified as:<sup>[30]</sup>

- i. **Normal polymerization:** It is a pure polymer formation technique but it is very difficult to dissipate the heat of reaction which affects the thermo labile active ingredients. Suspension polymerization is carried out of lower temperature and also refer to as pearl polymerization in which heating the monomer mixture with active drug as droplets dispersion in continuous aqueous phase. Microparticles size obtained by suspension techniques is less the 100  $\mu\text{m}$ .
- ii. **Interfacial Polymerization Method:** Interfacial polymerization technique is one in which two monomers, one oil-soluble and the other water-soluble, are employed and a polymer is formed on the droplet surface. The method involve the reaction of monomeric units located at the interface existing between a core material substance & a continuous phase in which the core material is dispersed.<sup>[31]</sup>

### 3. Superficial Antisolvent Precipitation Technique

This technique is useful if the drug is insoluble in gas & gas is soluble in liquid. The drug is dissolved in polymeric solution of suitable solvent. Then the application of an antisolvent decreases the solubility of material dissolved in solution leading to microparticle beads formation.

### 4. Particle Precipitation By Non Solvent Addition (Coacervation)

In this method microparticles are produced by dispersing either the solid crystal particles or an aqueous solution of the drug in an organic solution of polymer, followed by a phase separation by adding a second organic solvent in which the polymer is not soluble (defined here as a non solvent). That means the addition of a non solvent resulted in precipitation of the polymer around the aqueous solution of drug to form microparticles.<sup>[31]</sup>

### 5. Particle precipitation by solvent partitioning

In this method, a solution or suspension of the drug in the polymer/organic solvent solution is slowly injected into a stream of mineral oil. Since the organic solvent is soluble in the oil, but the drug and the polymer are not, co-precipitation of the drug and polymer occurs as the mixture partitions into the oil. The outcome will depend on the solubility of the drug. If the drug is soluble in the polymer solution, the drug and polymer precipitate together.<sup>[31]</sup> If the drug is suspended in the polymer solution, the polymer will precipitate around the solid drug particles.

### 6. Spray drying

Spray drying is used to protect sensitive substances from oxidation based on the atomization of a solution by compressed air and drying across a current of warm air. Microparticle formulation by spray drying is conducted by dispersing a core material in a coating solution, in which the coating substance is dissolved & in which the core material is insoluble, & then by atomizing the mixture into an air stream. The heated air causes removal of solvent from the coating solution thus causing formation of the microparticles.<sup>[31]</sup> Atomization, Mixing & Drying these three steps involved in spray drying.<sup>[27,29]</sup>

### 7. Reversed Micellar Method

Reverse micellar is the stable liquid mixture of oil, water, and surfactants dissolved in organic solvents. To this mixture, an aqueous solution of chitosan and the target molecule are added before the addition of a crosslinking agent such as glutaraldehyde.<sup>[30]</sup>

### 8. Iontropic External Gelation Technique

The alginate microparticles are prepared by ionotropic external gelation technique. In this method, weighed quantity of the drug is added to 50 ml of phosphate buffer solution (pH-7.4) containing the sodium alginate and thoroughly mixed with a stirrer at 400 rpm. For the formation of microparticles, 50 ml of this solution is extruded drop wise from a needle of 22 G in diameter from a height of about 6 cm into 100 ml aqueous calcium chloride solution and stirred at 100 rpm. Then the solution containing the gel formed microparticles is filtered by using Whatman filter paper no-1. The microparticles are allowed to dry at about 30- 40°C and stored in well closed container for further use.<sup>[30]</sup>

### 9. Suspension Cross Linking<sup>[32]</sup>

This involves dispersion of an aq. solution of the polymer containing core material in an immiscible organic solvent (suspension/dispersion medium), in the form of small droplet. The suspension medium contains a suitable stabilizer to maintain the individuality of the droplet/microcapsules. The cross linking process is accomplished either thermally (at >5000c) or by the use of a cross linking. It is a versatile method and can be adopted for microencapsulation of solution, insoluble, liquid or solid materials, and for the production of microcapsules.

### 10. Hot Melt Microencapsulation<sup>[32]</sup>

The polymer is first melted and then mixed with solid drug particle or liquid drugs. This mixture is suspended in an immiscible solvent and heated to 5°C above the melting point of the polymer under continuous stirring. The emulsion is then cooled below the melting point until the droplets solidify.

### ➤ APPLICATIONS OF MICROPARTICLES<sup>[32]</sup>

Microparticulate drug delivery offers several applications for drugs having poor bioavailability.

**Sustained Drug Delivery:** By encapsulating a drug in a polymer matrix, which limits access of the biological fluid into the drug until the time of degradation, microparticles maintain the blood level of the drug within a therapeutic window for a prolonged period. Toxic side effects can be improved by reducing the frequency of administration.

**Controlled Drug Delivery:** Here, the drug is delivered at a predetermined rate, locally or systemically for a specified period of time. Depot formulation of short acting peptide have been successfully developed using microparticle technology.

**Local Drug Delivery:** Subcutaneously or intramuscularly applied microparticles can maintain a therapeutically effective concentration at the site of action for a desirable duration. The local delivery system obviates systemic drug administration for local therapeutic affects and can reduce the related systemic side effects. It is proven beneficial for delivery of local anesthetics.

**Pulsatile Drug Delivery:** While burst and pulsatile release is not considered for sustained delivery application, their release pattern proves to be useful for delivery of antibiotics and vaccines. Pulsatile release of antibiotics can alleviate evolution of the bacterial resistance. In the vaccine delivery, initial burst followed by delayed release pulsed can mimic an initial and boost injection respectively. Potential application of this drug delivery system is replacement of therapeutic agents, gene therapy, and in use of vaccine for treating AIDS, tumors, cancer, and diabetes. The spheres are engineered to stick tightly to and even penetrate linings in the GIT before transferring their contents over time into circulatory system.

## CONCLUSION

From the study it can be concluded that Nasal drug delivery has generated interest as an alternative route for administration of drugs and biomolecules that are susceptible to enzymatic or acidic degradation and first pass metabolism & mucoadhesive drug delivery system enhances the nasal residence time of the drug molecule and hence enhances the absorption and bioavailability of nasally administered drug products.

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