# CHAPTER-1
# (INTRODUCTION)

In recent years growing attention has been paid to the nasal drug administration as an alternative route of administration for systemically active drugs such as proteins, peptides, hormones, and other drugs which are poorly absorbed orally and extensively metabolized in liver[1]. Nasal route is easily accessible, convenient and reliable route with a porous endothelial membrane and a highly vascularized epithelium that provides a rapid absorption of compounds into the systemic circulation, avoiding the hepatic first pass elimination. In addition, intranasal drug delivery enables dose reduction, rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects.

The gastrointestinal tract is the major route of administration to the systemic delivery. However for some drugs this route creates problems. The gastrointestinal tract presents hostile environment, it contain enzymes, a wide range of pH conditions and varies in its composition depending upon the presence or absence of food. Those drugs which are susceptible to either acid hydrolysis or extensive metabolism in liver may exhibit poor bioavailability when given through oral route.

Parentral route is the best route of administration to avoid this problem. However, it suffers from some problems as is associated with pain and discomfort and only can be given by medical personnel. Injectables need to be sterilized also and increases the cost. In addition certain health risks are associated with this route e.g. psychological distress, occasional allergies and hypertrophy or atrophy.

In an attempt to over these problems, alternative routes of drug administration had been investigated. Transdermal, rectal, buccal and nasal routes are other alternative routes for systemic delivery of drugs avoiding above problems to a great extent. However, transdermal route does not provide rapid blood level and is limited to controlled delivery of potent lipophilic drugs. The rectal route suffer from variable patient acceptance and depending upon the site of absorption, the drugs may be subjected to first pass effect. Buccal and sublingual routes of drug administration are of much interest, but sometime pose inconveniences during speaking, eating and drinking[2].

Hence, the nasal administration of drug is becoming increasingly important for systemic delivery of active drugs.

## 1.2 ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM

- Drug degradation that is observed in the gastrointestinal tract is absent.
- Hepatic first pass metabolism is absent.
- Rapid drug absorption and quick onset of action can be achieved.
- The bioavailability of large drug molecules can be improved by means of absorption enhancer or other approach.
- The nasal bioavailability for smaller drug molecules is good.
- Drugs that are orally not absorbed can be delivered to the systemic circulation by the nasal drug delivery.
- The existence of a rich vasculature and a highly permeable structure in the nasal mucosa for systemic absorption.
- The ease and convenience of intranasal drug administration.
- Venous blood from nose passes directly into systemic circulation.
- Nasal route eliminates the intersubject variation normally associated with oral route
- Intra nasal delivery is needle free, patient friendly administration route because needles are not involved, this method of drug delivery is virtually painless. For patients who fear injections, intranasal administration offers a more acceptable alternative. Additionally, the simplicity of nasal delivery would allow for self-administration in a sitting. In general, for patients, the intranasal dosage form provides comfortable, non-threatening, less invasive therapy. This may be important in young patient populations.
- Another major benefit of intranasal administration, in contrast to injectables, is that not contribute to biohazardous waste. When the drug has been delivered through intranasal administration devices may be disposed off in the normal garbage. This delivery method does not require needles, risk of accidental sticks is not a concern.
- From a pharmacokinetic standpoint, absorption is rapid, which should provide fast onset of action compared to oral and intramuscular administration. Hepatic first pass

metabolism is also avoided, allowing increased, reliable bioavailability. In this regard good drug candidates for nasal delivery are those that undergo extensive first pass metabolism, display erratic absorption, or require therapeutic onset.

- Patent life of a particular product may be extended via development of an alternative dosage form, providing companies the opportunity to maintain their market share. So from a drug development perspective, intranasal delivery should stimulate favourable outcomes[3].

## 1.3 ANATOMY AND PHYSIOLOGY OF NOSE

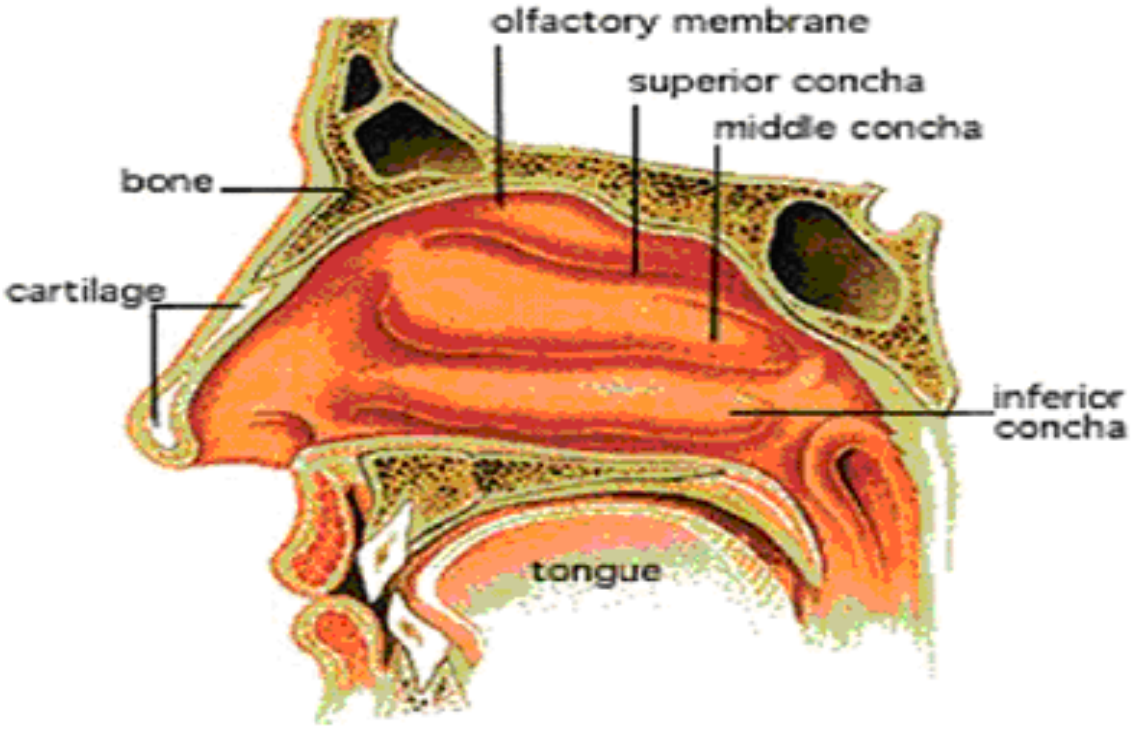
The nasal cavity is divided into two symmetrical halves by the nasal septum**,** a central partition of bone and cartilage each side opens at the face via the nostrils and connects with the mouth at the nasopharynx. The nasal vestibule, the respiratory region and the olfactory region are the three main regions of the nasal cavity.

The lateral walls of the nasal cavity include a folded structure, which enlarges the surface area in the nose to about 150cmsq. This folded structure includes three turbinates: the superior, the median and the inferior.

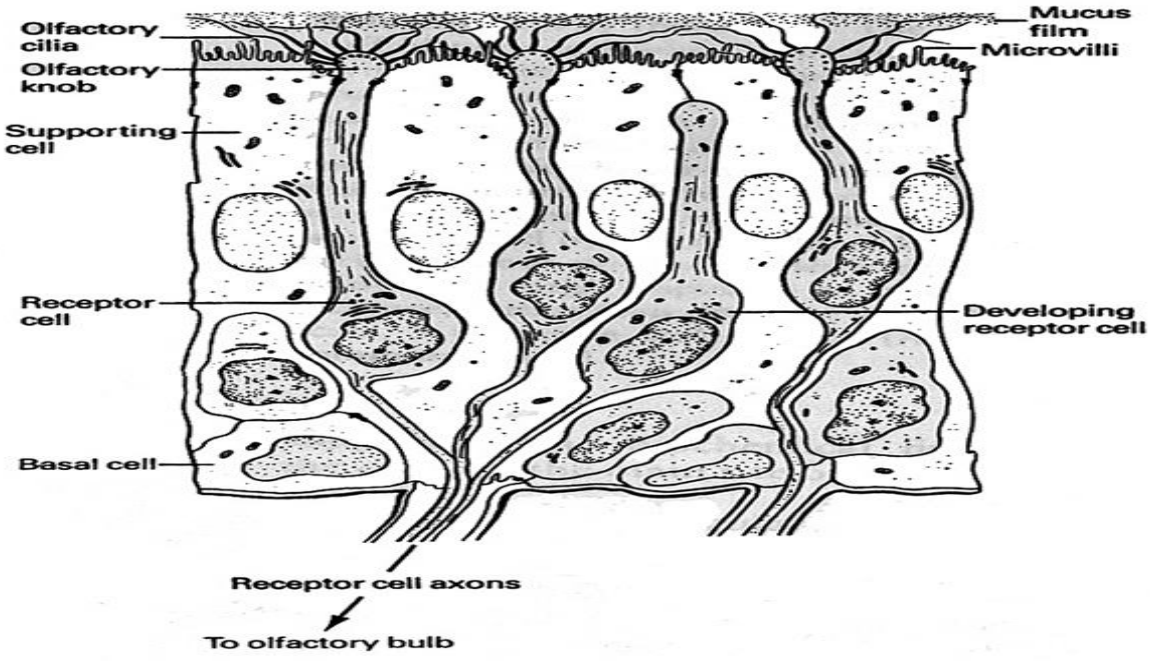
In the main nasal airway, the passages are narrow, normally only 1-3mm,and this narrow structure enables the nose to carry out its main function. During inspiration, the air comes into close contact with nasal mucosa and particles such as dust and bacteria are trapped in the mucous. Additionally, the inhaled air is warmed and moistened as it passes over the mucosa and the high blood supply in the nasal epithelium.

The submucosal zone of the nasal mucosa open directly to the systemic circulation, thus avoiding first pass metabolism. Another, perhaps more familiar, major function of the nose is olfactory region is located on the roof of nasal cavity.

The nasal cavity is covered with a mucous membrane which can be divided into nonolfactory areas includes the nasal vestibule, which is lined with skin like cells, and respiratory region, which has a typical airways epithelium[53].




Figurer. 1.1: A Representation Of The Human Nose




Figurer. 1.2: A Diagrammatic Cross section through nasal epithelium

**The respiratory region**

The nasal respiratory epithelium is generally described as a pseudo-stratified ciliated columnar epithelium. This region is considered to be the major site for drug absorption into the systemic circulation. The four main types of cells seen in the respiratory epithelium are ciliated columnar cells, non-ciliated columnar cells, goblet cells and basal cells. Although rare, neurosecretory cells may be seen but, like basal cells, these cells do not protrude into the airway lumen. The proportion of the different types of cells vary in different regions of the nasal cavity. In the lower turbinate area, about 15-20% of the total numbers of are ciliated and 60-70% is non-ciliated epithelial cells. The number of ciliated cells increase towards the nasopharynx with a corresponding decrease in non-ciliated epithelial cells.

The high number non-ciliated cells indicate their importance for absorption across nasal epithelium. Both columnar cells types have numerous (about300-400per cell) microvilli. The large number of microvilli increases the surface area and this is one of the main reasons for the relatively high absorptive capacity of the nasal cavity.

Cilia are hair like projections on the exposed surface of epithelial cells. Each cell has about 300 cilia, measuring about 5 to 10µm in length and 0.1-0.3µm in diameter. The cilia beats in regularways, with a frequency of 10Hz. Their role is to facilitate the movement of mucus from the nasal cavity to the nasopharynx, and ultimately to the DI tract, the combined effect being known as mucociliary clearance. The role of ciliated cells is to transport mucus towards the pharynx.

Basal cells which vary greatly in both number and shape, never reach the airway lumen. These cells are poorly differentiated and act as **s**tem cells. About 5-15% of the mucosal cells in the turbinates are goblet cells, which contain numerous secretory granules filled with mucin. In conjugation with the nasal glands the goblet cells produce secretions, which form the mucus layer.

**The olfactory region**

In human, the olfactory region is located on the roof of the nasal cavities just below the cribriform plate of the ethmoid bone, which separates the nasal cavities from the cranial cavity. The olfactory tissue is often yellow in colour, in contrast to the surrounding pink tissue. Human have relatively simple noses, since the primary function is breathing, while other mammals have more complex noses better for the function of olfaction.

Outer gel layer of the mucus, moving it towards the nasopharynx, and then disengaging and returning to their starting position through the serous inner layer. The turnover time for mucus is variously quoted as approximately 10-15 mins in total and 20 mins for the half-life of mucociliary clearance.

Mucus presents a difffusional barrier to the drug absorption, and any formulation must be able to overcome this, as well as remain in the region long enough to allow drug release and absorption. Various strategies for achieving these goals are given later, but it is important that any interruption to mucociliary clearance, whether from drug or excipient, should be minimal and temporary[4].

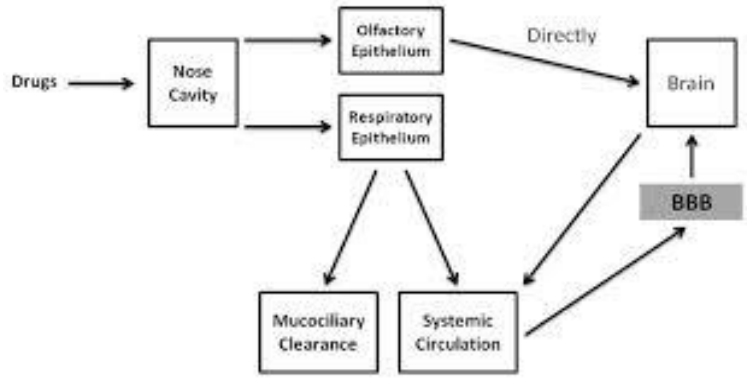



Figure 1.3 : Drug absorption form nose

## 1.4 FACTORS AFFECTING NASAL DRUG ABSORPTION

Various factors affect bioavailability of nasally administered drugs as follows:-

**I - Biological Factors**

• Structural features

• Biochemical changes

**II - Physiological factors**

• Blood supply and neuronal regulation

• Nasal secretions

• Mucociliary clearance and ciliary beat frequency

• Pathological conditions

• Environmental conditions.

• Membrane permeability.

**III- Physicochemical Properties of Drugs**

• Molecular weight

• Size

• Solubility

• Lipophilicity

• pka and Partition coefficient

• Chemical form of drug.

• Polymorphism.

• Chemical state.

• Physical state.

**IV- Physicochemical Properties of Formulation**

• Physical form of formulation

• pH

• Osmolarity

• Volume of solution applied and drug concentration

• Viscosity.

**I - Biological factors**

**1] Structural features-** There are five different sections of nasal cavity: nasal vestibule, atrium, respiratory area, olfactory region and the nasopharnyx. These structures and the

type of cells, density and number of cells present in that region influence the permeability. Absorption enhancers used in combination with drugs increase the permeation of compounds.

**2] Biochemical changes-** Enzymatic barrier to the delivery of drugs is nasal mucosa because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes, peptidases and proteases. These enzymes are responsible for the degradation of drugs in the nasal mucosa and result in creation of a pseudo-first-pass effect. Metabolism of nasal decongestants, alcohols, nicotine and cocaine is due to p450 dependent monoxygenase system. Protease and peptidase were responsible for the presystemic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin. To overcome these degradations various approaches have been used. These include the use of protease and peptidase inhibitors such as bacitracin, amastatin, boroleucin and puromycin .

**II -Physiological factors**

**1] Blood supply and neuronal regulation -**Nasal mucosa is highly permeable site. High blood supply due to parasympathetic stimulation gives congestion and low blood supply due to sympathetic stimulation gives relaxation, regulate the rise and fall in the amounts of drug permeated, respectively. Based on the above observations, we can conclude that the increased permeability of a compound is due to parasympathetic stimulation.

**2] Nasal secretions-** Nasal secretions are produced by anterior serous and seromucus glands. Mucus production is approximately 1.5–2 l ml daily. The permeability of drug through the nasal mucosa is affected by:

• **Viscosity of nasal secretion** The viscous surface layer will inhibit the ciliary beating if the sol layer of mucus is too thin and mucociliary clearance is impaired if sol layer is too thick, because contact with cilia is lost. Permeation of the drug is affected due to impairment of mucociliary clearence by altering the time of contact of drug and mucosa.

• **Solubility of drug in nasal secretions** For permeation of drug solublisation is necessary. A drug needs to have appropriate physicochemical characteristics for dissolution in nasal secretions.

• **Diurnal variation** Nasal secretions are also affected by circadian rhythm. Permeation of drug is altered at night due to secretions and clearancerates are reduced. Chronokinetics dictate the pattern and rate of permeation in such cases.

• **pH of nasal cavity** variation in pH is observed between 5.5–6.5 in adults and 5.0–7.0 in infants. Permeation of drug is greater if the nasal pH is lower than pKa of drug because under suchconditions the penetrant molecules exist as unionized species. Increase or decrease in the permeation of drug is observed because ionization is affected by change in pH of mucus, depending on the nature of the drug. pH of formulation should be between 4.5 to 6.5 for better absorption and should also have good buffering capacity.

**3] Mucociliary clearance (MCC) and ciliary beating-** Whenever a substance is nasally administered, it is cleared from the nasal cavity in ~21 min by MCC because mucociliary clearance is the normal defense mechanism of the nasal cavity which clears substances adhering to nasal mucosa and cleared in GIT by draining into nasopharynx. Drug permeation is enhanced by increasing contact time between drug and mucus membrane because reduced MMC; whereas, increased MCC decreases drug permeation.

**4] Pathological conditions-** Mucociliary disfunctioning, hypo or hypersecretions, irritation of the nasal mucosa occurs due to diseases such as the common cold, rhinitis, atrophic rhinitis and nasal polyposis, and drug permeation is affected by this.

**5] Environmental conditions-** Moderate reduction in the rate of MCC occurs at the temperature of 24oC, it has been predicted that a linear increase in ciliary beat frequency occurs with increase in temperature.

**6] Membrane permeability-** Absorption of the drug through the nasal route is affected by membrane permeability which is most important factor. The large molecular weight drugs and water soluble drugs like peptides and proteins have low membrane permeability hence absorbed through endocytic transport in fewer amounts

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**III Physicochemical properties of drug**

**1] Molecular weight and size-** Drug permeation is determined by molecular weight, molecular size, hydrophilicity and lipophilicity of the compound. For compounds 1 kDa, bioavailability can be directly predicted from knowledge of MW. In general, the bioavailability of these large molecules ranges from 0.5% to 5%. Physicochemical properties of the drug don't significantly affect permeation of drug LT 300 Da, which will mostly permeate through aqueous channels of the membrane. By contrast, for compounds with MW 300 Da rate of permeation is highly sensitive.

**2] Solubility-** Major factor in determining absorption of drug through biological membranes is drug solubility. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Lipophilic drugs have less solubility in the aqueous secretions. Water soluble drugs are absorbed by passive diffusion and lipophilic drugs via active transport depending on their solubility.

**3] Lipophilicity-** The permeation of the compound normally increases through nasal mucosa with increase in lipophilicity. It appears that nasal mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes although they have some hydrophilic characteristics. Systemic bioavailability of many drugs is decreased due to excess hydrophilicity in such cases prodrug approach is beneficial.

**4] pKa and partition coefficient-** As per the pH partition theory, unionized species are absorbed better compared with ionized species and the same fact is true in the case of nasal absorption. There is constant relationship between pKa and nasal absorption of

these drugs. With an increase in lipophilicity or the partition coefficient of the drugs its concentration in biological tissues increases. The absorption rate of aminopyrine increased with the increase in pH and was found to fit well to the theoretical profile Major factor governing nasal absorption is partition coefficient.

**5] Polymorphism-** Polymorphism is the important parameter in the nasal drug product development which is administered in particulate form. Polymorphism is known to affect dissolution of drugs and their absorption through biological membranes is affected by polymorphism. This factor should be carefully considered in the dosage form developmentfor the nasal delivery.

**6] Chemical state of drug-** Absorption of the drug is determined by the chemical form of the drug in which it is presented to nasal mucosa. Chemically alter a drug molecule by adding a bio-cleavable lipophilic moiety is the alternative for improving absorption of the drug which is not having desired absorption properties. The prodrug approach provides many additional challenges which need to be overcome in the drug product developmental process. The toxicity of the prodrug itself needs to be fully evaluated .

**7] Physical state of drug-** Particle size and morphology of drug are two main important properties for particulate nasal drug products. These both parameters should be controlled

to obtain suitable drug dissolution properties in the nostrils. Too fine particles below 5 microns should be avoided because it may get inhaled in lungs. Generally, particles in the 5–10 micron range are deposited in the nostrils.

**IV Physicochemical properties of formulation:**

**1] Physical form of formulation:-** Physical form of the formulation is very important in nasal drug absorption. Liquid formulations are less effective than powder form in delivering insulin in rabbits. Less efficient systemic nasal drug delivery observed with more viscous formulation. Scientist found that somewhat more sustained effects of

desmopressin are observed with addition of viscous agent but total bioavailability is not enhanced. Viscous formulations may help in minimizing nasal drip.

**2] pH-** extent of drug ionization is determined by pH partition hypothesis hence it is related to formulation pH. Nasal formulation should be adjusted to appropriate pH to avoid irritation, to obtain efficient absorption and to prevent growth of pathogenic bacteria. Ideal formulation pH should be adjusted between 4.5 and 6.5. pH of the nasal surface is 7.39 and the pH of nasal secretions is 5.5–6.5 in adults and 5.0–6.7 in infants and children.

**3] Osmolarity-** Formulation tonicity substantially affect the nasal mucosa generally, an isotonic formulation is preferred. Some scientist studied the effects of formulation osmolarity, on the nasal absorption of secretin in rats. They found that all cells of the nasal mucosa were affected by the concentration of sodiumchloride in the formulation and-the absorption reached a maximum at a 0.462 M sodium chloride concentration. At this concentration shrinkage of epithelial cells was observed. Hence tonicity is also having impact on drug absorption.

**4] Volume of solution applied and drug concentration-** There is no constant relationship between volume of administration and extent of absorption. Clement studied the effect of three nasal spray concentrations of cetrizine on the clinical efficacy. The results showed that 16.7%, 30.8%, 42.9%, and 26.7% of days the patients experienced appeared to improve with the drug concentration up to only 0.125%. At the higher concentration, 0.250%, the efficacy declined.

**5] Viscosity-** Contact time between the drug and the nasal mucosa is increased by higher viscosity of formulation thereby increasing the time for permeation.

**Types of nasal drug delivery systems:**

The selection of delivery system depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences. Some of these delivery systems and their important features are summarized below:

- **Nasal drops:**

Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

- **Nasal sprays:**

Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 µl. The particles size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

- **Nasal gels:**

Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing device, there was not much interest in this system. The advantages of a nasal gel includes the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target to mucosa for better absorption.

- **Nasal powder**:

This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particles size, aerodynamic properties and nasal irritancy of the active drug and /or excipients. Local application of drug is another advantage of this system[3, 5]

## 1.5 LIMITATIONS OF NASAL ADMINISTRATION

The nasal drug administration also has certain limitations.

- Rapid mucociliary clearance
- Enzymatic degradation
- Lower absorption

- **Nasal metabolism**

The nasal route of administration avoids hepatic first pass metabolism, but nasal mucosa does possess enzymatic activity as a protective mechanism against exogenous chemicals. Nasal first pass metabolism may be a significant factor in the absorption of some drugs. For example, there is high content of cytochrome P450 enzymes, P450 monooxygenases can oxidizes many nasally administered drugs, such as nasal decongestants and anesthetic.

There are many other types of enzymes in the nasal mucosa, which can act on conventional drugs.

Example includes dehydrogenases, hydroxlases, carboxylesterases, carbonic anhydrases, and various phases II conjugative enzymes .The development of new nasal dosage forms should therefore include some considerations of the nature, extent and location of the drug's metabolism in the nose. Not all metabolism is undesirable, however, and certain enzymes, such as esterases, open the possibility of using prodrugs as a mean of improving nasal delivery.

- **Mucociliary clearance**

Mucociliary clearance is a non-specific defensive function which also presents a barrier to the drug absorption. The mucus layer is normally 5-20μm thick, consisting of mainly water containing glycoproteins, ions and various other proteins such as enzymes and immunoglobulins. Glycoprotein gives the mucus its viscous character, which causes foreign particles to become trapped, cleared to the GI tract, and ultimately eliminated from the body. The mucus is actually divided into two layers, the one closest to the cell surface being a less viscous, the watery substance. This aids clearance by the lubricants

the passage of the mucus over the cell surface and easing the action of cilia. The cilia work in ratchet like way by engaging the viscous[53].

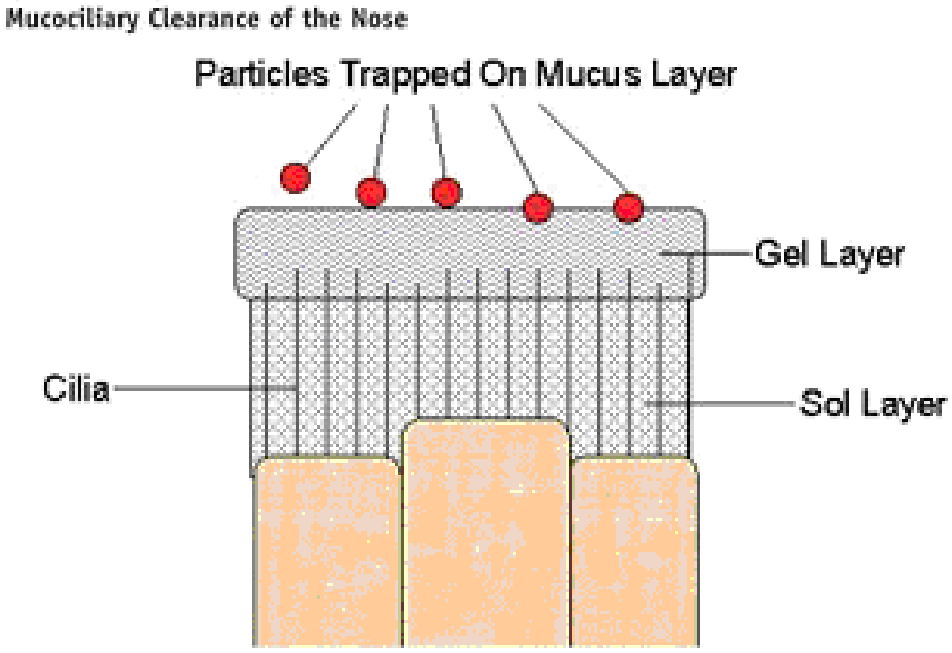



**Figure. 1.4: Mucociliary Clearance Of The Nose**

**The three major approaches that have been attempted are:**

- Incorporation of enzyme inhibitors.
- Use of chemical enhancer to improve absorption.
- Increasing the drug local residence time[6].

**Enzyme inhibition**

Substances like bile salts (e.g. sodium glycocholate) and surfactants (e.g. polyoxy-9-lauryl ether) in combination with drug modify the properties of nasal mucosa, inhibiting the enzyme activity in the nasal membrane and reduce the viscosity of mucous thereby

allow for an easier diffusion of the drug through this layer, thereby enhancing absorption of drugs[7].

**Enhancing nasal absorption:**

The mechanism of action of absorption enhancer is increasing the rate at which drug passes through the nasal mucosa. Many enhancers act by altering the structure of epithelial cells in some way, but they should accomplish this while causing no damage or permanent change to nasal mucosa.

General requirement of an ideal penetration enhancer are as follows.

1. It should lead to an effective increase in the absorption of the drug.

2. It should not cause permanent damage or alteration to the tissue.

3. It should be non irritant and nontoxic.

4. It should be effective in small quantity.

5. The enhancing effect should occur when absorption is required.

6. The effect should be temporary and reversible.

7. It should be compatible with other excipients.

- **Classification of penetration enhancer:**

Chemical penetration enhancers are widely used in the nasal drug delivery. Classification of chemical penetration enhancer includes, following

- Solvents
- Alkylmethylsulphoxides
- Pyrrolidones
- 1-Dodecylazacycloheptan-2-one
- Surfactants.

**Mechanism of penetration enhancers is as follows:-**

• Increasing cell membrane permeability.

• Opening tight junction and formation of intracellular aqueous channels.

•Increasing lipophilicity of the charged drug by forming ion pair

• Inhibiting proteolytic activity.

The focus of present work is to prevent the rapid clearance of the delivery system from the nasal cavity and thereby prolong the contact between the drug and nasal mucosa by using bioadhesive formulations.

A major modification of the intranasal formulation is the use and incorporation of bioadhesive technology.

Recently, a mathematical model was developed describing the rate processes involved in the nasal drug delivery. Using this model the effect of bioadhesive carrier systems can be stimulated by reducing the mucociliary clearance rate constant for the transport from the posterior of the nose to the nasopharynx.

These stimulations predicted that bioadhesion may improve systemic bioavailability and reduce the variability in the nasal drug absorption as caused by a variable pattern of drug retention.

## 1.6 BIOADHESIVE CONTROLLED DRUG DELIVERY

Bio-adhesion is defined as a state in which two bodies, one or both of which are of biological nature, are hold together for extended period of time by interfacial force, or bio-adhesion is defined as the ability of the material (synthetic or biological) to adhere to a biological tissue for an extended period of time.

For drug delivery purposes, the polymer /drug carrier is usually a non biological macromolecular or hydrocolloid material that adheres primarily to mucus layer or alternatively may attach to the underlying epithelium

The delivery system which utilizes property of bioadhesion of certain water soluble 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.

Technology has improved to such a level that dosage forms could deliver drugs for days to years. Despite these advances, long-term drug delivery via many routes, especially the oral route, has been limited. Regardless of the time period for drug release from the device, the extent of drug absorption is determined in many instances by the residence time of the device at the absorption site. Thus, the advantages of controlled- release drug delivery have not been fully appreciated.

Extensive efforts have recently been focused on targeting a drug or drug delivery system in a particular region of the body for extended period of time, not only for local targeting of drugs but also for the better control of systemic drug delivery.

## 1.7 ADVANTAGES OF BIOADHESIVE SYSTEMS

Bioadhesive systems have three distinct advantages when compared to conventional dosage forms:

- The bioadhesive systems are readily localized in the region applied to improve and enhance the bioavailability of drugs.

- These dosage forms facilitate intimate contact of the formulation with underlying absorption surface.

- The bioadhesive dosage forms also prolong residence time of the dosage form at the site of application and absorption to permit once or twice a day dosing.

- A polymeric device also allows for slow, controlled and predictable drug release overtime and reduces the initial drug loading concentration needed. This reduction also decreases the toxicity and waste of expensive drugs as well as improves patient compliance[5].

## 1.8 FACTORS AFFECTING BIOADHESION

The bioadhesive power of a polymer is affected by the nature of the polymer and also by the nature of the surrounding media. The factors influencing the bioadhesion are summarized below[8]:

**1.Polymer related factors**

- Molecular weight
- Concentration of active polymer
- Flexibility of polymer chains
- Spatial confirmation
- Swelling

**2. Environment related factors**

- pH of polymer-substrate interface
- Applied strength
- Initial contact time

**3. Physiological factors**

- Mucin turnover
- Disease state

## 1.9 MECHANISM OF BIOADHESION

For bioadhesion to occur, a succession of phenomena, whose role depends on the nature of the bioadhesive, is required. The first stage involves an intimate contact between a bioadhesive and a membrane, either from a good wetting of the bioadhesive surface, or from the swelling of the bioadhesive. In the second stage, after contact is established, penetration of the bioadhesive into the crevices of the tissue surface or interpenetration of the chains of the bioadhesive with those of the mucus takes place. Low chemical bonds can then settle.

To explain the fundamental mechanisms of adhesion. In a particular system one or more theories contribute to the formation of bioadhesive bonds.

Proposed theories of bioadhesion include wetting, diffusion, electronic, adsorption and fracture [9,10]

**1.Wetting[11]**:

This theory bests describes the adhesion of liquid of paste to a biological surface. The work of adhesion can be expressed in terms of surface and interfacial tension ($\gamma$) being defined as the energy per $cm^2$ released when an interface is formed. According to Dupre's equation[12]. The work of adhesion is given by—

$$Wa = \gamma_A + \gamma_B - \gamma_{AB} \quad (1)$$

Where the subscript A and B refer to the biological membrane and the bioadhesive formulation respectively. The work of cohesion is given by---

$$Wc = 2\gamma_A \text{ or } 2\gamma_B \quad (2)$$

For a bioadhesive material B spreading on a biological substrate A the spreading coefficient is given by

$$S_B/_A = \gamma_A - (\gamma_B + \gamma_{AB}) \quad (3)$$

$S_B/A$ should be positive for a bioadhesive material to adhere to a biological membrane. For a bioadhesive liquid B adhering to a biological membrane A the contact angle is given by

$$\text{Cos } \theta = (\gamma_A - \gamma_{AB}/\gamma_B) \quad (4)$$

**2. Diffusion[13]**:

Voyutski appears to be the first to discuss diffusion, as a theory for adhesion. According to this theory the polymer chains and the mucus commingle to a sufficient depth to create a semi-permanent adhesives bond. Additional insight as to the mechanism of interpenetration has recently been provided by Prager and Tirrell. The bioadhesive material and glycoprotein of the biological membrane are brought in close contact. The polymer chains penetrate the mucus; the exact depth to which it penetrates to achieve sufficient mucoadhesion depends on the diffusion coefficient, time of contact, and other experimental variables. The diffusion coefficient depends on molecular weight and decreases rapidly as the cross-linking density increases. Flexibility of the bioadhesive polymer and mucus glycoproteins molecules plays an important role in bioadhesion due to the need for commingling of chains to increase the area of contact.

In summary the molecular weight, chain flexibility, expanded nature of both the mucoadhesive and substrate as well as similarity in chemical structure are required for good mucoadhesion.

*1.* **Electronic** [14]: The electronic theory of adhesion was suggested by Derjaguin and Smilga According to this theory electron transfer occurs on contact of an adhesive polymer and the mucus glycoproteins network because of differences in their electronic structure. This results in formation of an electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer. Such a system behaves analogous to a capacitor, which is charged when two different surfaces come in contact, and discharged when they are separated.

*2.* **Fracture[11]**: The fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by

$$\sigma = (E \in / L)\ ½ \qquad (5)$$

Where E is Young's modulus of elasticity $\in$ is the fracture energy and L is the critical crack length when two surfaces are separated. The work of fracture of an elastomer network Gc is given by-

$$Gc = K\ (Mc)\ ½ \qquad (6)$$

K is a constant dependant on density of the polymer, effective mass, length, and flexibility of a single mucin chain bond, and bond dissociation energy. Gc of an elastometric network increases with molecular weight Mc of the network stands.

3. **Adsorption[9]:** Adsorption theory has been described by Kemball and Huntsberger. According to this theory after an initial contact of the two surfaces the material will adhere because of surface forces acting between the atoms in the two surfaces. Weak interaction, of Vander wall type, plays an important role. However if adsorption is due to chemical bonding i.e. chemisorption, then ionic, covalent and metallic bonds play an important role at the interface.

**Interaction mechanisms of bioadhesion**

Adhesion of a polymer to a tissue involves contribution from three main regions

- The surface of the bioadhesive material
- The first layer of the natural tissue
- The interfacial region between the two layers

Adhesion between a polymer and tissue is primarily due to three types of interactions.

- Physical or mechanical bonds
- Chemical bonds or ionic
- Primary or covalent chemical bonds[15]

## 1.10 BIOADHESIVE POLYMERS

Bioadhesive polymers include water-soluble polymers and water-insoluble polymers which are swellable networks joined by cross linking agents. Bioadhesion is dependent on the nature of the polymer that acts as an adherent to the biological membrane. Bioadhesion process requires two criteria; the polymer should possess optimal polarity to make sure it is sufficiently 'wetted' by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

An ideal polymer for a mucoadhesive drug delivery system should have the following characteristics:-

**1.** The polymer and its degradation products should be non-toxic and non absorbable from the gastrointestinal tract.

**2.** It should be a nonirritant to the mucous membranes.

**3.** It should preferably form a strong noncovalent bond with the mucin epithelial cell surfaces.

**4.** It should adhere quickly to moist tissue and should possess some site specificity.

**5.** It should allow easy incorporation of the drug and offer no hindrance to its release.

**6.** The polymer must not decompose on storage or during shelf life of the dosage form. The cost of the polymer should not be high, so that the prepared dosage form remains competitive[16].

- **Nature of bioadhesive polymer**

**A. Molecular weight and chain length**

It was reported that bioadhesive strength increases as the molecular weight of a polymer increases upto 100,000. Also, it was found that the molecular weight of

Sodium carboxymethyl cellulose should exceed 78,600 in order to provide significant bioadhesion. Thus, there appears to be a critical molecular weight requirement for significant bioadhesion. For the majority of polymers, an increase in molecular length, which will in turn influence bioadhesion via its effect on the interpenetration and entanglement of the polymer to the substrate. The bioadhesive property of polyethylene oxide increased, essentially no bioadhesion at a molecular weight of 40, 00,000. On the other hand, dextrans with molecular weights as high as 195, 00,000 have been reported to have similar bioadhesive strength to those with a molecular weight of 200,000.

**B. Charges and ionization**

Results from various studies showed that when both bioadhesiveness and cellular toxicity were considered, polyanionic polymers were preferred over polycationic and neutral polymers. Furthermore, based primarily on limited toxicity data, polyanions with carboxyl groups seemed to be better candidates than those with sulfate groups.

In studying the bioadhesive strength of the poly (acrylic acid) hydrogels (pKa=4.75), it was reported that bioadhesion was favoured when carboxylic groups were in undissociated form and available for formation of hydrogen bonds. Furthermore polymer chain should be flexible enough to form as many hydrogen bonds as possible. Thus depending on the pKa of bioadhesive materials, the strength of adhesion can be maximized by controlling the degree of bioadhesion by manipulation of the media pH, or alternatively a bioadhesive with pKa that can provide a low degree of ionization at a chosen pH can be used.

**C. Hydrophilic functional groups and hydration**

Bioadhesive polymers have hydrophilic functional groups that can form hydrogen bonds, e.g., carboxyl, hydroxyl, amide and sulfate groups. Hydrogen bonding seems to play a dominant role and hence, the amount of water presents at the interface between the adhesive polymers and biological membrane and/or mucous is critical for the bioadhesion and or mucoadhesion. When bioadhesives hydrate in aqueous media, they swell and form a gel. The rate and extent of water uptake by the mucoadhesive depends

on the type and number of hydrophilic functional groups present in the polymer structure, as well as the pH and ionic strength of the aqueous medium. It was found that as the percent composition of charge on a polymer decreases, the degree of hydration decreases. Swelling time is an important parameter for assessing bioadhesiveness the quicker a polymer is hydrated, the faster will be initiation of diffusion, formation of bonds and an entangled interface; and thus the quicker the initiation of the bioadhesive behavior. It has been reported that excessive swelling results in abrupt drop in the adhesive strength.

**D. Chain segment mobility**

The ability of the polymer chains to interpenetrate can be approximated by their ability to diffuse. Thus, the chain segment mobility of a polymer, and perhaps mucin can be related to their viscosity and diffusion coefficients. The diffusion coefficients show an exponential temperature dependency, which makes bioadhesion a temperature dependant process.

The strength of bioadhesion has been found to decrease with an increase in concentration of the cross linking agent. An increase in cross-linking density decreases the diffusion coefficient, chain segment flexibility and mobility, thereby reducing the extent of interpenetration. Bioadhesion is also a time dependant process. As the contact time increases, the depth of interpenetration and thus the strength of adhesion increase.

**E. Expanded nature of polymer network**

The number and size of the pores in the hydrated network will affect the diffusion and interpenetration process can be approximated by their ability to diffuse. Thus, the chain segment mobility of a polymer, and perhaps mucin, can be related to their viscosity and diffusion coefficients. The diffusion coefficients show an exponential temperature dependency, which makes bioadhesion a temperature dependant process. The strength of bioadhesion has been found to decrease with an increase in concentration of the cross linking agent. An increase in cross-linking density decreases the diffusion coefficient, chain segment flexibility and mobility, thereby reducing the interpenetration. As the

contact time increases, the depth of interpenetration and thus the strength of adhesion increase.

**F. Concentration of bioadhesive polymer**

There seems to exist an effective concentration to optimize bioadhesion. In highly concentrated systems, the adhesive strength drops significantly. In a concentrated solution the coiled molecules become solvent-poor and the available chain length for interfacial penetration decreases significantly. Excessive crosslinking of the polymer does not contribute to boiadhesion for the same reasons. But for the solid dosage forms such as tablets, found that increased concentration of the polymer resulted in higher bioadhesion strengths.

When polymeric adhesive delivery systems are placed in an aqueous medium, the polymer network absorbs a significant amount of water to form a gel. It has been shown that the rate of release of drug can be controlled by the hydration rate and crosslinking density of the polymer network, the solubility of the active ingredient, and the addition of hydrophilic or lipophillic excipients[17].

## *1.11 MICROPARTICULATE DELIVERY SYSTEM*

The drug should be delivered to specific target sites at a rate and concentration that permit optimal therapeutic efficacy while reducing side effects to minimum. The microparticulate delivery systems are considered and accepted as a reliable means to deliver the drug to the target site with specificity, if modified, and to maintained the desired concentration at the site of interest without untoward effect(s).

A method for achieving controlled release in solid dosage form is by creating a physical barrier whereby retarding the release of drug molecules. This can be accomplished in two ways:-

(i) Embedding the drug in the polymer matrix in a homogenous manner (monolithic micromatrices)

(ii) Coating the drug core with a polymeric membrane (reservoir microcapsules).

The term microcapsule, is defined as a spherical particle with size varying from 50 nm to 2mm, containing a core substance

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1-1000µm.The two types of microspheres are: -

(a) Microcapsule, where the entrapped substance is completely surrounded by a distinct wall and

(b)Micromatrices, where the entrapped substance is dispersed throughout the microsphere matrix.

Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug.

These carriers received much attention not only for prolonged release but also for the targeting of the anticancer drugs to the tumour[18].

**Prerequisites for ideal microparticulate carriers**

- Longer duration of action
- Control of content release
- Increase of therapeutic efficiency
- Protection of drug
- Reduction of toxicity
- Biocompatibility
- Sterilizability
- Relative stability
- Water dispersibility or solubility
- Bioresorbability
- Targetability
- Polyvalent

The potential use of microspheres in the pharmaceutical industry has been considered since the 1960s for the following applications:

- Taste and odor masking.
- Conversion of oils and other liquids to solids for ease of handling.
- Protection of drug against the environment (moisture, light, heat, and/or oxidation) and vice versa. (Prevention of pain on injection).
- Delay of volatilization.
- Separation of incompatible materials (other drugs or excipients such as buffers).
- Improvement of flow of powders.
- Safe handling of toxic substances.
- Aid in dispersion of water- insoluble substances in aqueous media, and Production of sustained-release, controlled-release, and targeted medications.
- Reduce dose dumping potential compared to large implantable devices[18].

## 1.12 GENERAL METHODS OF PREPARATION

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

1. The particle size requirement.
2. The drug or protein should not be adversely affected by the process.
3. Reproducibility of the release profile and the method.
4. The stability and the biological activity should not be affected.
5. There should be no toxic product(s) associated with the final product.
6. The process should be usable at industrial scale.
7. Yield and drug encapsulation efficiency should be high.
8. Microspheres should not exhibit aggregation or adherence[18].

## Some of the general methods of preparations are:

### Solvent evaporation

A buffered or plain aqueous solution of the drug (may contain 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 emulsions (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

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 50μm. The mixture is suspended in a non-miscible solvent (like silicon oil), continuously stirred, and heated to $5^0$ 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 μm 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**

It is a non-aqueous method of microencapsulation, particularly suitable for water labile polymers such as the polyanhydrides. 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 silicon oil containing span 85 and methylene chloride. After pouring the polymer solution into silicon 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**

Microspheres made of gel-type polymers, such as alginates, 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 the gelled microspheres. The method involves an all-aqueous system, which eliminates 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**

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 coalesence 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.

**Emulsification phase separation technique:-**

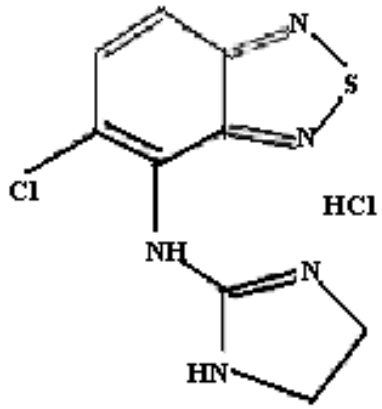
Mucoadhesive microspheres of chitosan were prepared by simple emulsification phase separation technique.100mL of paraffin oil mixture of 50mL heavy liquid paraffin and 50mL light liquid paraffin oil was placed in 500mL plastic beaker. Chitosan 200mg was dissolved in 2% acetic acid solution. The drug 100mg was added in it and the suspension was extruded through syringe in 100ml of liquid paraffin containing 0.2% DOSS(dioctyl sulfosuccinate). This addition was accompanied with stirring of paraffin oil with the help of high-speed stirrer (Remi stirrer) After 20 minutes of stirring, 1ml of glutaraldehyde (25%, solution as cross linking agent) was added and stirring was continued for 3 hours after the complete addition of chitosan solution into oil.

Suspension of chitosan microspheres in paraffin oil thus obtained were allowed to stand to let the microspheres settle down under gravity. Clear supernatant liquid was decanted and microspheres obtained as residue were washed 3-4 times with the solvent cyclohexane to remove oil and finally washed with water to remove excess of glutaraldehyde. After the final wash, microspheres were allowed to dry in air. Dry powder thus obtained was collected and stored in desiccator at room temperature[19]

## 1.16 DRUG PROFILE[4, 20, 21, 22, 23]

**DRUG-Tizanidine HCl**

- **Chemical structure-**




- **Chemical name:** 6α-fluro-11β, 16α, 17, 21tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with acetone, hemihydrate.
- **Molecular formula**: $C_{24}H_{31}FO_6$
- **Molecular weight**: 443.51
- **Melting point**: 245°C
- **Log P/Hydrophobicity**: 0.63
- **Solubility State:** Freely soluble in methanol, chloroform, water, 5% acetic acid. Practically insoluble in liquid paraffin light and heavy.

**SPECIFICATION:-**

- **Identification** : 97.0-102.0%
- **Loss on drying** : NMT 1.0%
- **Water content** : NMT 1.0%
- **Residue on ignition** : NMT 0.1%

**Drug category:** Anti asthamatic agents
Anti-inflammatory agents

**Pharmacology**

These are drugs which reduce skeletal muscle tone by a selective action in the cerebrospinal axis, without altering consciousness. They selectively depress spinal and supraspinal polysynaptic reflexes involved in the regulation of muscle tone without significantly affecting monosynaptically mediated stretch reflex. Polysynaptic pathways in the ascending reticular formation which are involved in the maintenance of wakefulness are also depressed, though to a lesser extent.

**Mechanism of action**

Tizanidine is an agonist at □2-adrenergic receptor sites. It inhibits release of excitatory amino acids in spinal interneurons. It may facilitate the inhibitory transimitter glycine as well. It inhibits polysynaptic reflexes; reduces muscle tone and frequency of muscle spasms without reducing muscle strength.In animal models, tizanidine has no direct effect on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons.

The imidazoline chemical structure of tizanidine is related to that of the anti-hypertensive drug clonidine and other □2-adrenergic agonists. Pharmacological studies in animals show similarities between the two compounds, but tizanidine was found to have one-tenth to one-fiftieth (1/50) of the potency of clonidine in lowering blood pressure

**Adverse effects**

Dry mouth, hoarseness, sore throat and pharyngeal, laryngeal or tracheal candidiasis sometimes occurs after continuous use.

**Pharmacokinetics**

| | |
|---|---|
| **Absolute bioavailability** | 40 %( PERORAL) |
| **Protein binding** | 30% |
| **Biotransformation** | primarily hepatic, converted to S-β-OH metabolite |
| **Half life** | 2.5 Hrs |

## 1.17 EXCIPIENT USED IN MICROSPHERE PREPARATION [9, 19, 24, 25]

**GLUTARAL**

**Pentanedial: Glutaraldehyde: Glutaric Dialdehyde: Cidex**

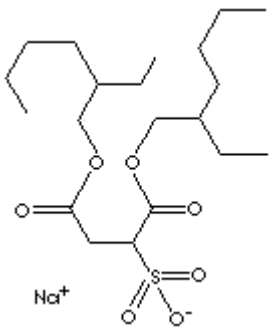
**$OCH(CH_2)_3CHO$, $C_5H_8O_2$**

**Preparation** The 1:1 Diels-Alder adduct of acrolein and Vinyl alkyl ether is hydrolysed, forming glutaral and an alkanol.

**Description** Colourless liquid; pungent odor; boils about $188^0$C with decomposition; stable in light; oxidizes in air; polymerizes on heating.

*Solubility* ***Soluble in water and in alcohol.***

**DOCUSATE SODIUM**




**Nonproprietary Names** BP: Docusate sodium

PhEur: Docusatum natricum

USP: Docusate sodium

**Synonyms** Bis(2-ethylhexyl)sodium sulfosuccinate; dioctyl sodium sulfosuccinate; DSS; sodium dioctylsulfosuccinate;sulfo-butanedioic acid 1,4-bis(2-ethylhexyl) ester,sodium salt.

**Chemical Name** Sodium 1, 4-bis(2-ethylhexyl)sulfosuccinate

**Empirical formula** $C_{20}H_{37}NaO_7S$

**Molecular weight** **444.56**

**Functional category** anionic surfactant, wetting agent.

**Application** Docusate sodium and docusate salts are widely used as anionic surfactants in pharmaceutical formulations.

**Description** Docusate salt is a white or almost white, wax like, bitter tasting, plastic solid with a characteristic octanol like odor. It is hygroscopic and usually available in the form of pellets, flakes, or rolls of tissue-thin material.

**PROPERTIES:**

- **Acidity/ alkalinity**: pH = 5.8-6.9(1% w/v aqueous solution).
- **Acid value:** < 2.5
- **Critical micelle concentration:** 0.11 % w/v aqueous solution at $25^0$
- **Density :** 1.16gm/$cm^3$
- **Hydroxyl value:** 6.0-8.0
- **Iodine number** : $\leq$ 0.25
- **Melting point:** 153-157$^0$C
- **Moisture content:** 1.51%
- **Saponification value:** 240-253
- **Solubility :** Soluble in acetone and vegetables oils freely soluble in glycerine

**Stability and storage conditions**

Docusate sodium salt is stable in the solid state when stored at room temperature. Dilute aqueous solutions of docusate sodium between pH 1-10 are stable at room temperature. However at very low pH(<1) and very high pH (>10) docusate sodium solutions are subject to hydrolysis.

The solid material is hygroscopic and should be stored in an airtight container in cool, dry place.

## LIQUID PARAFFIN, HEAVY

- **Nonproprietary Names** BP: Liquid paraffin
  PhEur: Paraffinium liquidium
  USP: mineral oil
- **Synonyms** 905(mineral hydrocarbons); Avatech; Drakeol; heavy mineral oil; heavy liquid petrolatum; paraffin oil; Sirrius; white mineral oil

- **Chemical Name** Mineral oil

- **Empirical formula** Mineral oil is a mixture of refined liquid saturated aliphatic ($C_{14}$ **-$C_{18}$)** and cyclic hydrocarbons obtained from petroleum.

- **Functional category** Emollient; lubricant; oleaginous vehicle; solvent.

- **Application** Mineral oil is used primarily as an excipient in topical pharmaceutical formulations, where its emollient properties are exploited as an ingredient in ointment bases. It is additionally used in oil-in-water emulsions, as a solvent, as a lubricant in capsule, tablet and ophthalmic formulations, and to a limited extent as a mold-release agent for cocoa butter suppositories. More recently it has been used in the preparation of microspheres.

- **Description** Mineral oil is a transparent, colourless, viscous oily liquid without fluorescence in daylight. It is practically tasteless and odorless when cold, and has a faint odor of petroleum when heated.

**PROPERTIES**

- **Boiling point:** $> 360^0$
- **Flash point** 210-224
- **Pour point** -12.2 to $-9.4^0$C
- **Refractive index** 1.4756-1.4800
- **Surface tension** 35Mn/M AT $25^0$C
- **Solubility** practical insoluble in ethanol (95%), glycerine, and water; soluble in acetone; benzene, chloroform, carbon disulfide, ether, and petroleum ether. Miscible with volatile oils and fixed oils, with the exception of castor oil.
- **Viscosity** 10-230mPa s at $20^0$C.

**Stability and storage conditions**

Mineral oil undergoes oxidation when exposed to heat and light. Oxidation begins with the formation of peroxides, exhibiting an 'induction period'. Oxidation results in the formation of aldehydes and organic acids, which impart taste and odor. Mineral oil may be sterilized by dry heat.

It should store in an airtight container, protected from light, in a cool dry place.

## LIQUID PARAFFIN, LIGHT

- **Nonproprietary Names** BP: light Liquid paraffin
  PhEur: Paraffinium perliquidium
  USPNF: Light mineral oil
  JP: Light liquid paraffin

- **Synonyms** 905(mineral hydrocarbons); Citation;
  light liquid petrolatum light white mineral oil

- **Chemical Name** Light Mineral oil

- **Empirical formula** Light Mineral oil is a mixture of refined liquid saturated hydrocarbons obtained from petroleum. It is less viscous and has lower specific gravity than mineral oil.

- **Functional category** Emollient; oleaginous vehicle; solvent, tablet and capsule Lubricant; therapeutic agent.

- **Application** Light mineral oil is used in applications similar to those of mineral oil. Mineral oil is used primarily as an excipient in topical pharmaceutical formulations, where its emollient properties are exploited as an ingredient in ointment bases. It is also used in ophthalmic formulations. Light mineral oil is additionally used in oil-in-water and polyethylene glycol/glycerol emulsions; and as the oily medium used in the microencapsulation of many drugs. Light mineral oil is also used in cosmetics and certain food products. More recently it has been used in the preparation of microspheres.

- **Description** Light Mineral oil is a transparent, colourless liquid, without fluorescence in daylight. It is practically tasteless and odorless when cold, and has a faint odor of petroleum when heated.

**PROPERTIES**

- **Solubility** Soluble in chloroform, ether, hydrocarbon
  Sparingly soluble in ethanol (95%); practically insoluble in water.

- **Stability and storage conditions**

Mineral oil undergo oxidation when exposed to heat and light. Oxidation begins with the formation of peroxides, exhibiting an 'induction period'. Oxidation results in the formation of aldehydes and organic acids, which impart taste and odor. Mineral oil may be sterilized by dry heat.
It should store in an airtight container, protected from light, in a cool dry place.

**CHITOSAN**

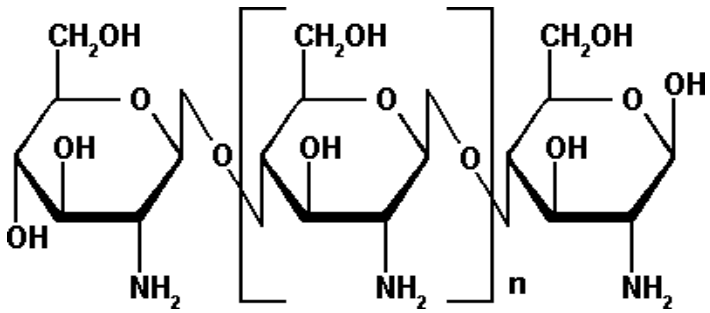



**Figure 1.5: Chemical structure of chitosan**

Chitosan is a fibre-like substance derived from chitin, a homopolymer of β-(1 4) -linked N-acetyl-D-glucosamine. Being biodegradable and biocompatible, chitosan has been used in the formulation of particulate drug delivery. Chitin is the second most abundant organic compound in nature after cellulose. Chitin is widely distributed in marine invertebrates, insects, fungi, and yeast. Chitin is widely available from a variety of source among which, the principal source is shellfish waste such as shrimps, crabs, and crawfish. It also exists naturally in a few species of fungi.

With regards to their chemical structure, chitin and chitosan have similar chemical structure. Chitin is made up of a linear chain of acetylglucosamine groups while chitosan is obtained by removing enough acetyl groups ($CH_3$-CO) for the molecule to be soluble in most diluted acids. This process is called deacetylation. The actual difference between chitin and chitosan is the acetyl content of the polymer. Chitosan having a free amino group is the most useful derivative of chitin.

- **Characteristics of Chitosan**

Chitosan is a non-toxic, biodegradable polymer of high molecular weight, and is very much similar to cellulose, a plant fiber. The only difference between chitosan cellulose is the amine(-$NH_2$ ) group in the position C-2 of chitosan instead of the hydroxyl (-OH) group found in the cellulose.

- **Degree of Deacetylation**

The process of deacetylation involves the removal of acetyl groups from the molecular chain of chitin, leaving behind a compound (chitosan) with a high degree chemical amino group (-$NH_2$). This makes the degree of deacetylation an important property in chitosan production as it affects the physiochemical properties.

- **Molecular Weight**

Chitosan is a biopolymer of a high molecular weight. Like its composition the molecular weight of chitosan varies with the raw material sources and the method of preparation. Molecular weight of native chitin is usually larger than one million Daltons while commercial chitosan products have the molecular weight range of 100,000-1,200,000 Daltons, depending on the process and grades of the product. In general, high

temperature, dissolved oxygen, and shear stress can cause degradation of chitosan. For instance at a temperature over $280^0$C, thermal degradation of chitosan occurs and polymer chains rapidly break down, thereby lowering molecular weight. The molecular weight of chitosan can be determined by methods such as chromatography, light scattering, and viscometry.

- **Viscosity**

Chitosan viscosity decreases with an increased time of demineralization. Viscosity of chitosan in acetic acid tends to increase with decreasing pH but also decrease with decreasing pH in HCl, giving rise to the definition of 'Intrinsic Viscosity' of chitosan, which is a function of the degree of ionization as well as ion strength. Chitosan viscosity is considerably affected by physical (grinding, heating, autoclaving, ultrasonication) and chemical (ozone) treatments, except for freezing, and decreases with an increase in treatment time and temperature. Chitosan solution stored at $4^0$C is found to be relatively stable from a viscosity point.

- **Solubility**

While chitosan is insoluble in most organic solvents, chitosan is readily soluble in dilute acidic solutions below pH 6.0.Organic acids such as acetic, formic, and lactic acids are used for dissolving chitosan. The most commonly used is 1% acetic acid solution at about pH 4.0 as a reference. Chitosan is also soluble in 1% hydrochloric acid but insoluble in sulfuric and phosphoric acids. Solubility of chitosan in inorganic acids is quite limited. Above pH 7.0 chitosan solubility's stability is poor. The solubility, however, is controlled by the degree of deacetylation and it is estimated that deacetylation must be at least 85% complete in order to achieve the desired solubility.

- **Bulk Density**

The bulk density of chitin from shrimp and crab is normally between 0.06 and 0.17g/mL.

- **Color**

Chitosan powder is quite flabby in nature and its color varies from pale yellow to white whereas starch and cellulose powder have smooth texture and white color.

Chitin is a (1-4) linked 2-acetamido-2-deoxy-β-D-glucan,a structural polysaccharide, is distributed plentiful in nature. It is highly hydrophobic materials insoluble in water as well as most organic solvents but by deacetylation it is possible to increase its aqueous solubility. Chitin is main component of shells, crabs, shrimp and krill.

Chitosan (1-4) linked [2-acetamido-2-deoxy-β-D-glucan] is a partially, N-deacylated product of the polymer, chitin, its aqueous solubility being dependent upon the degree of deacetylation which can be varied according to the intended use.

Chitosan is a cationic, hydrophilic, polyelectrolyte which has one amino and hydroxyl groups, which are able to react chemically with drugs and other bioactive substances.

Chitin and chitosan are biocompatible and biodegradable compounds easily degraded by enzymes and the degradation products are non-toxic.

Chitosan was originally used as a natural flocculant for waste water treatments. Several high and Welfare approved the use of both chitosan and carboxymethyl chitin as ingredients for hair and skin care products.

The use of chitin fabrics as artificial skin cover for burn was also approved and the commercial product is on sale. Chitin Suture, which is digestable in our tissues, has been manufactured by a Japanese company.

Chitosan has been gaining increasing importance in the pharmaceutical field owing to its good biocompatibility, non-toxicity and biodegradability. It is used in the food industry, in cosmetics and as a bioadhesive in numerous pharmaceutical applications in the form of beads, microspheres, and microcapsules, typically for the prolonged release of the drugs, proteins, and DNA