Chapter-1

INTRODUCTION

Over the few decades, advances in the in-situ gel technologies have spurred development in many medical and biomedical applications including controlled drug delivery. Many Novel In-Situ gel based delivery matrices have been designed and fabricated to fulfill the ever increasing needs of the pharmaceutical and medical fields. Nasal drug delivery system is a recent advancement in the drug administration technology. It offers various advantages over conventional drug delivery systems. An adult nasal cavity has about a 20 ml capacity with a large surface area (about 180 cm^2) for the drug absorption afforded by the microvillus present along the pseudo-stratified columnar epithelia cells of the nasal mucosa [(1)] . In therapeutics, nose forms an important part of the body for faster and higher level of drug absorption with the possibility of self-administration. Drugs are ranging from small micromolecules to large macromolecules such as peptide/proteins, hormones, and vaccines, are being delivered through the nasal cavity. It is reported that lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profiles often identical to those obtained following an intravenous injection with a bioavailability approaching up to 100% in many cases. Large absorption surface area and high vascularization lead to fast absorption. In emergency, nasal route can be used as a substitute route of parenteral administration [(2-5)].

Oral drug delivery is the most desirable route for the drug administration. Whenever systemic effects are indented but oral bioavailability of some compounds has promoted the search of more effective route for the systemic delivery. Trans mucosal route of drug delivery (i.e. the mucosal lining of the nasal, rectal, vaginal, ocular, oral cavity) nasal mucosa is the major route of administration to achieve faster and higher level of drug absorption [(6)].

Nasal mucosa has been considered as a potential administration route to achieve faster and higher levels of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents [(7,8)]. In recent years many drugs especially large hydrophilic peptides and proteins have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal therapy is the recognized form of treatment in the Ayurvedic systems of Indian medicine, and also called as Nasaya Karma [(9)].

Relatively less residence time of the drug in nasal cavity affects its bioavailability. The possible strategy to improve the residence time is to decrease the rapid mucociliary clearance using mucoadhesive formulations. However, for ordinary gels and mucoadhesive powders, residence time cannot be enhanced due to the following drawbacks: accurate drug dose cannot be measured due to difficulty in administration and nasal mucosa irritation and a gritty appearance of the tissues respectively [(12,13)] . The use of in situ nasal gels has been found to be an attractive alternative to overcome the drawbacks associated with ordinary gels and muco-adhesive powders.

Among the different nasal drug delivery systems, in situ gel formulations have been explored for both local and systemic drug delivery. These drug delivery systems exist in sol form before their administration; however, once administered, they undergo gelation to form a gel. The factors regulating the in situ gel formation process include microenvironment temperature, changes in pH,

presence of ions, ultraviolet irradiation, and polymers. Rheological properties of gels, which are critical to their efficacy, are important in retaining the gel at the site of application or absorption [14]. In-situ is a Latin term which means „In its original place or in position". In-situ gel is a type of dosage form in which the medicament is in solution form before administration into the body, after administered it undergoes gelation to form a gel. Due to its accessibility, nasal drug administration is considered as an alternative route for systemic circulation instead of intravenous administration[10] . For large molecular weight drugs or hydrophilic drugs show low bioavailability or no absorption due to the less permeable to the protease drugs in the nasal membrane so the drugs cleared rapidly before reaching the blood stream that is the drug does not pass through the mucosal barrier. Penetration enhancers such as surfactants, bile salts and phospholipids increases the drug penetration but in site of clinical use the toxicity test proved that the permeation enhancers has some limitation due their irreversible damage. Even though the number of challenges for the researchers to overcome some disadvantages in conventional nasal products and to make effort for the new nasal formulation [11] .

ANATOMY AND PHYSIOLOGY 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 [35]. 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 [36] . The zones are arranged anteroposteriorly in the sequence of order. The vestibular area serves as a baffle system and its surface is covered by a common pseudostratified epithelium where the long hairs may provide the function of filtering air borne particles. Respiratory area has a surface lined by a pseudostratified 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 [36] .The olfactory segment is lined with a specialized type of pseudostratified 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 axons of the bipolar neurons form the olfactory nerve (cranial nerve I). Bowman's glands are serous glands in the lamina propria, whose secretions trap and dissolve odoriferous substances [37] .

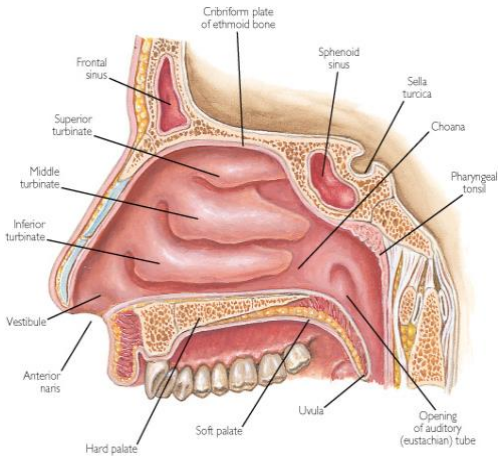

Fig. 1. The lateral Nasal wall

The total surface area of both nasal cavities is about 150 cm^2 and the total volume is about 15 ml. Approximately 1.5 cm from the nares (nostrils) is the narrowest portion of the entire airway, the internal ostium (or nasal valve) with a cross-sectional area of about 30 mm^2 on each side. The nasal valve accounts for approximately 50% of the total resistance to respiratory airflow from the nostril to the alveoli [37] . 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). 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 inferior and middle meatus receive the openings of the nasolacrimal duct and the paranasal sinuses. The mucous membrane in a meatus will not be hit by an ordinary intranasal spray. The individually variable caliber and shape of the lumen of the nasal cavities make it difficult to give uniform recommendations for intranasal drug administration [35] .

Nasal Epithelium

The nostrils are covered by skin, the anterior one-third of the nasal cavity by a squamous and transitional epithelium, the upper part of the cavity by an olfactory epithelium and the remaining portion by a typical airway epithelium which is ciliated, pseudostratified and columnar [35] .

The epithelial cells in the nasal vestibule are stratified, squamous and keratinized with sebaceous glands. Due to its nature, the nasal vestibule is very resistant to dehydration and can withstand noxious environmental substances and limits permeation of substances. The atrium is a transitional epithelial region with stratified, squamous cells anteriorly and pseudostratified columnar cells with microvilli posteriorly [38] .

The nasal airway epithelium consists of four major cell types: basal cells, ciliated and non-ciliated columnar cells, goblet cells and basement membrane. Basal cells are the progenitors of the other cell types and lie on the basement membrane and do not reach the airway lumen. They are believed to help in the adhesion of columnar cells to the basement membrane. Columnar cells are related to neighbouring cells by tight junctions apically and in the uppermost part by interdigitations of the cell membrane. All columnar cells, ciliated and non-ciliated are covered by about 300 microvilli uniformly distributed over the entire apical surface. These short and slender fingers like cytoplasmic expansions increase the surface area of the epithelial cells thus promoting exchange processes across the epithelium. The microvilli also prevent drying of the surface by retaining moisture essential for ciliary function. The cilia have a typical ultra structure, each ciliated cell containing about 100 cilia, 0.3 µm wide and 5 µm in length. The anterior one-third of the nasal cavity is non-ciliated [38] .

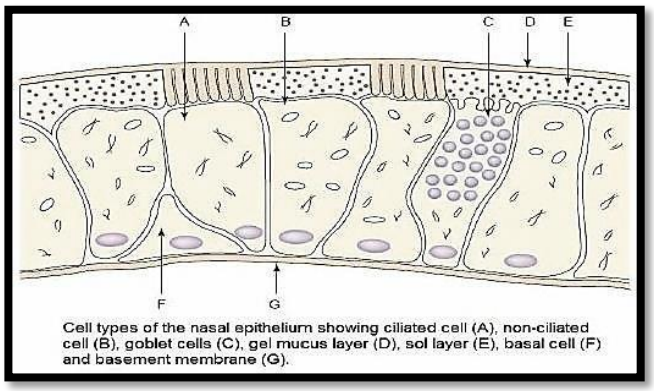

Fig. 2. Structure of the Nasal Epithelium

Cilia start occurring just behind the front edge of the inferior turbinate and the posterior part of the nasal cavity as well as the paranasal sinuses is densely covered by cilia. Another cell type, characteristic of an airway epithelium is the goblet cell. The goblet cell contribution to the volume of nasal secretion is probably small compared to that of the submucosal glands. Goblet cells probably respond to physical and chemical irritants in the microenvironments. The basement membrane is the layer of the collagen fibrils on which the epithelium rests [35] . The olfactory epithelium is a pseudostratified columnar in type and consists of specialized olfactory cells, supporting cells and both serous and mucous glands. The olfactory cells are bipolar neurons and act as peripheral receptors and first-order ganglion cells [36] .

Blood Supply to Nasal Cavity [28]

Nasal vasculature is richly supplied with blood to fulfill the basic functions of the nasal cavity such as heating and humidification, olfaction, mucociliary clearance and immunological functions. 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.

The lamina propria in the nasal mucosa is rich in blood vessels. They differ from the vasculature in the tracheobronchial tree in three ways. First is venous sinusoid in the nose. Second is arteriovenous anastomosis in the nose. Third are the nasal vasculature shows cyclical changes of congestion giving rise to the nasal cycle. Porosity of the endothelial basement membrane has been described as a characteristic of nasal blood vessels. The capillaries just below the surface epithelium and surrounding the glands are well suited for rapid movement of fluid through the vascular wall.

Mucus Secretion and Mucociliary Clearance [39]

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 which swell in the nasal fluids to contribute to the mucus layer. 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 to 2 litre of nasal mucus is produced daily. This mucus blanket about 5 mm thick consists of two layers, a lower sol layer and an upper gel layer. The viscosity of both layers affects ciliary beating and the efficiency of transporting the overlying mucus, the mucociliary clearance (MCC). The nasal mucus performs a number of physiological functions,

Region	Structural features	Permeability
Nasal vestibule	-Nasal hairs (vibrissae) -Epithelial cells are stratified, squamous, and keratinized Sebaceous glands present	Least permeable due to the presence of keratinized cells, very resistant to hydration and can withstand insults from noxious substances of the environment.
Atrium	-Transepithelial region -Stratified squamous cells present anteriorly and pseudostratified cells with microvilli present posteriorly The narrowest region of the nasal cavity.	Less permeable as it has small surface area and stratified cells are present anteriorly.
Respiratory region (inferior turbinate middle turbinate superior turbinate)	-Pseudostratified ciliated columnar cells with microvilli (300 per cell), large surface area -Receives maximum nasal secretions due to the presence of seromucous glands, nasolacrimal duct, and goblet cells -Richly supplied with blood for heating and humidification of inspired air, the presence of paranasal sinuses	Most permeable region due to large surface area and rich vasculature
Olfactory region	Specialized ciliated olfactory nerve cells for smell perception Receives ophthalmic and maxillary divisions of the trigeminal nerve	Direct access to cerebrospinal fluid
Nasopharynx	The upper part contains ciliated cells, and the lower part contains squamous epithelium	Receives nasal cavity drainage

Table 1: Structural features of various regions and their impact on the permeability of nasal cavity [28-32]

- It covers the mucosa and physically and enzymatically protects it.
- The mucus has water-holding capacity.
- It exhibits surface electrical activity.
- It permits efficient heat transfer.
- It acts as adhesive and transports particulate matter towards the nasopharynx.
- It behaves as an adhesive.
- It acts as a retainer for the substances in the nasal duct.

Nasal ciliary clearance is one of the most important physiological defence mechanisms of the respiratory tract to protect the body against any noxious materials inhaled from reaching the lungs.

POSSIBILITIES FOR THE USE OF THE NASAL CAVITY FOR DRUG DELIVERY

The easy accessibility and available surface area make the nose a possibly viable drug delivery organ. Pharmaceutical product development is an essential task which is directly dependent on its therapeutic objectives. The aspects to be considered for product development depend on whether it is intended for:

a) Local delivery

b) Systemic delivery

c) Single or repetitive administration.

a) Local delivery

Nasal delivery is a logical delivery choice for local (or topical) treatment as it provides the minimal potential for systemic adverse effects when compared to the oral route of administration, and hence, relatively low doses are effective when administered through nasal route with less systemic toxic effects. Prominent therapeutic classes of drugs delivered are decongestants for cold nasal symptoms and antihistamines and corticosteroids for allergic rhinitis [15,16].

b) Systemic delivery

The intranasal administration of drugs is an effective way for the systemic availability of drugs as compared to oral and intravascular routes of administration. It provided fast and extended drug absorption than oral and parenteral administration. Therapeutic classes of drugs delivered include analgesics (exmorphine), cardiovascular drugs as propranolol and carvedilol, hormones such as levonorgestrel, progesterone, and insulin, anti-inflammatory agents as indomethacin and ketorolac, and antiviral drugs (acyclovir). Some examples which are available in the market include zolmitriptan and sumatriptan for the treatment of a migraine and cluster headaches [15, 17-21].

c) Nasal vaccines

During inhalation nasal mucosa is the first site of contact with inhaled antigens, and therefore, its use for vaccination, especially for respiratory infections, has been extensively evaluated. In fact, nasal vaccination is a promising alternative to the classic parenteral route because it can enhance the systemic levels of specific immunoglobulin G and nasal secretory immunoglobulin A. Examples of the human efficacy of intranasal vaccines include those against influenza A and B virus, proteosoma-influenza, adenovirus-vectored influenza, Group B meningococcal native, attenuated respiratory syncytial virus, and parainfluenza 3 virus [15, 22-25].

MECHANISM FOR DRUG PERMEATION [26 ,27]:-

The first step in the absorption of drug from the nasal cavity is passage through the mucus. Small unchanged particles easily pass through this layer. However, large or charged particles may find it more difficult to cross. Mucin the principle protein in the mucus has the potential to bind to solutes and hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.). Subsequent to a drug's passage through the mucus, 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.

• 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.

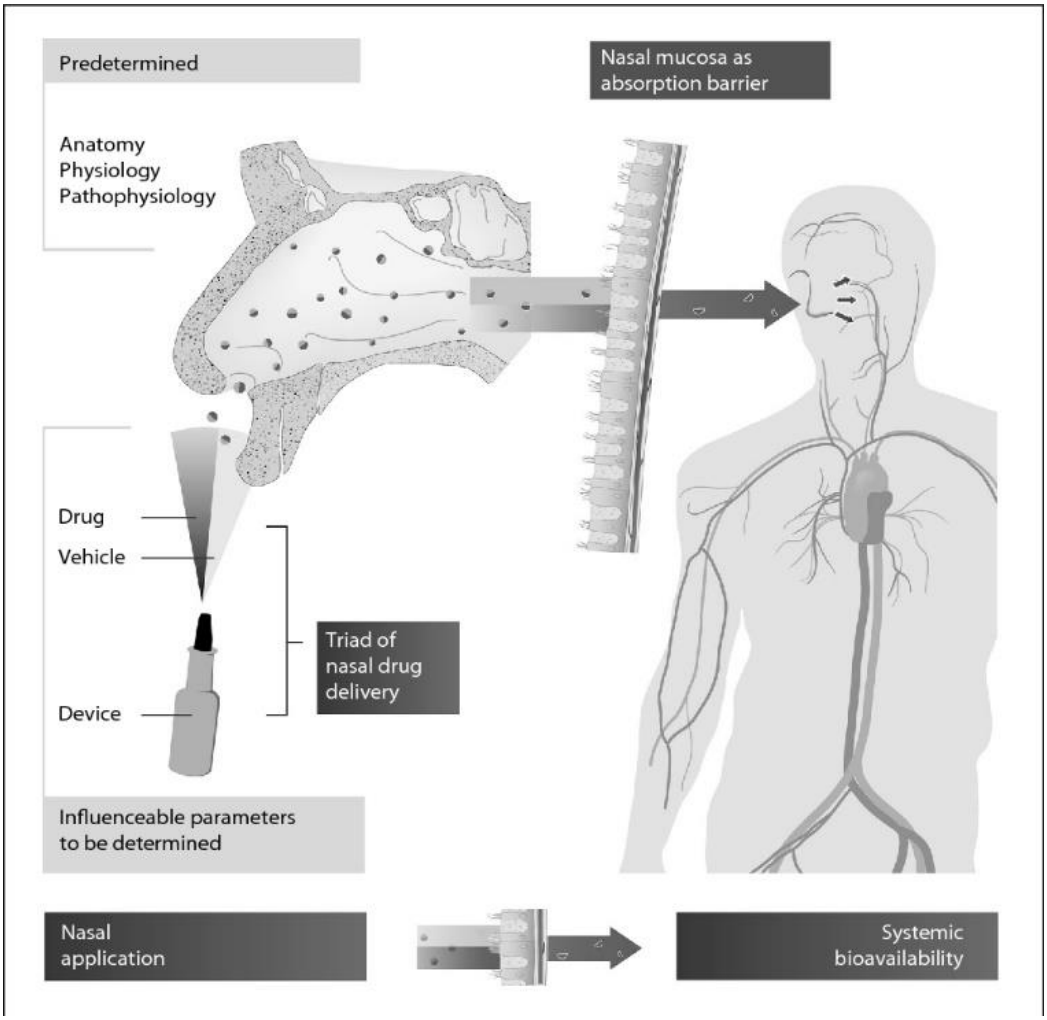

Fig. 3. Consideration of all elements in a formulation triad – comprising drug, vehicle form/system and delivery device

FACTORS AFFECTING NASAL DRUG ABSORPTION:-

Factors influencing absorption are related to nasal physiology, physicochemical characteristics of drugs and formulation aspects [26,28].

I. Biological Factors [28]

- Structural features
- Biochemical changes
  - Physiological factors
  - Blood flow
  - Nasal secretions
  - pH of the nasal cavity
  - Mucociliary clearance and ciliary beat frequency
- Pathological conditions
- Environmental factors
  - Temperature
  - Humidity

II. Physicochemical Properties of Drugs [28]

- Molecular weight
- Size
- Solubility
- Lipophilicity
- Pka and Partition coefficient

III. Physicochemical Properties of Formulation [26]

- Dosage form
- Viscosity
- pH and mucosal irritancy
- Osmolarity
- Volume of solution applied

IV. Device Related Factors [26]

- Particle size of the droplet/powder
- Size and pattern of disposion

I.BIOLOGICAL FACTORS

Physiological factors include firstly mucociliary clearance is one of the major factor responsible for the clearance of the drugs from the nasal cavity and it involves combined action of mucus layer and cilia, tips of cilia are in contact with and transport the superficial viscoelastic mucus layer towards nasopharynx while less viscous lower layer of mucus is relatively stationary. Secondly broad ranges of metabolic enzymes are present in the nasal mucosa. This can limit bioavailability of nasally administered drugs however; level of activity of these enzymes is lower as compared to that found in GIT and liver. Moreover pathological conditions like rhinitis, common cold can also affect absorption of drugs from nasal cavity and pH of nasal cavity also affects permeation of drug. A change in the pH of mucus can affect the ionization and increase or decrease the permeation of drug depending on the nature of the drug.

II.PHYSICOCHEMICAL PROPERTIES OF DRUGS

Various physicochemical characteristics of drug can also affect nasal absorption of the drug. Molecular Weight and Size Extent of the absorption of the drug depends on molecular weight particularly for hydrophilic compounds. Nasal route is suitable for efficient delivery of drugs up to 1000 Daltons. Absorption reduces the significantly if the molecular weight is greater than 1000 Daltons except with the use of penetration enhancers. It has been reported that a good linear correlation exists between the log percentage drug absorbed nasally and the log molecular weight of water soluble compounds suggestion the participation of aqueous channels in the nasal absorption of water soluble molecules. It has been reported that particle size greater than 10 µm are deposited in the nasal cavity. Particles that are 2 to 10 µm can be retained in the lungs and particles of less than 1 µm are exhaled.

Solubility and Dissolution

Drug solubility is a major factor in determining absorption of drug through biological membranes. It not only limits the drug absorption but it can also limit a formulator's ability to formulate a product if the drug is not sufficiently soluble in the desired vehicles. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Particles deposited in the nostrils need to be dissolved prior to absorption. If the drug remains as particles in nostrils or if they are cleared away from the nasal cavity, one may not observe absorption of the drug.

Chemical Form

The chemical form in which a drug is presented at the nasal mucosa can be important in determining its absorption. For example, conversion of a drug into a salt or ester form can alter its absorption. This phenomenon is associated with the increase in lipophilicity following esterification which increased the rate and extent of nasal absorption.

Partition Coefficient and pKa

A quantitative relationship between the partition coefficient and nasal absorption is constant. As per the pH partition theory, unionized species are absorbed better compared with ionized species and same holds true in the case of nasal absorption. The extent of absorption is PH dependent, being higher at a pH lower than the pKa and decreases beyond the pKa. In general, the authors found that the nasal absorption increase with the lipophilicity of the permeant. Various studies indicate that the drug concentrations in the cerebrospinal fluid (CSF) rise with an increase in lipophilicity or partition coefficient of the drugs.

III. PHYSICOCHEMICAL PROPERTIES OF FORMULATION

Drug Concentration, Dose and Dose volume

Drug concentration, dose and dose volume of administration are three interrelated parameters that impact the performance of the nasal delivery system. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. In general, higher nasal absorption or therapeutic effect was observed with increasing dose. It is important to note how the dose is varied. If the drug is increasing by increasing formulation volume there may be a limit as to what extent nasal absorption can be increased. The nostrils can retain only a limited volume beyond which a formulation will drain out of the nasal cavity. The ideal dose volume range is 0.05-0.15 ml with an upper limit of 0.20 ml.

Physical Form of Formulation

Nasal drug absorption depends on the physical form of the formulation. The important parameter in formulation development is viscosity of the formulation. Generally a more viscous formulation will provide less efficient systemic nasal drug delivery. In nasal delivery of desmopressin, addition of the viscous agents may produce a somewhat more sustained effect. It would seem logical that more viscous formulations e.g. gels should be more appropriate for locally acting drugs.

Formulation pH

The pH of the formulation as well as that of nasal surface can affect a drug's permeation. The pH of the nasal formulation is important for the following reasons,

- To avoid irritation of the nasal mucosa.
- To allow the drug to be available in unionized form for absorption.
- To prevent the growth of pathogenic bacteria in the nasal passage.
- To maintain functionality of excipients such as preservatives.
- To sustain normal physiological ciliary movement.

Lysozymes are found in nasal secretions which are responsible for destroying certain bacteria at acidic pH. Under alkaline conditions lysozyme is inactivated and the nasal tissue is susceptible to microbial infection. It is therefore advisable to keep the formulation at a pH of 4.5 to 6.5.

Buffer Capacity

Nasal formulations are generally administered in small volumes ranging from 25 to 200 µl with 100 µl being the most common dose volume. Hence, nasal secretions may alter the pH of the administered dose. This can affect the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH.

Osmolarity

Drug absorption can be affected by tonicity of the formulation. Shrinkage of the epithelial cells has been observed in the presence of hypertonic solutions. Hypertonic saline solutions also inhibit or cease ciliary activity. Low pH has a similar effect as that of hypertonic solutions. Generally an isotonic formulation is preferred.

Gelling / Viscofying Agents or Gel Forming Carriers

Some formulations need to be gelled or made more viscous to increase nasal residence time. Increasing the solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations. Drug carrier such as hydroxypropylcellulose was effective for improving the absorption of low molecular weight drugs but did not produce the same effect for high molecular weight peptides. Use of a combination of carriers is often recommended from a safety (nasal irritancy) point of view.

Solubilizers

Aqueous solubility of a drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol, medium chain glycerides and Labrasol can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrins such as HP-β-Cyclodextrins that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers. In such cases, their impact on nasal irritancy should be considered.

Preservatives

Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzyl alcohol are some of the commonly used preservatives in nasal formulations.

Antioxidants

Depending upon the stability profile of a given drug in the formulation chosen, it may be necessary to use antioxidants to prevent drug degradation. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylated hydroxy toluene and tocopherol.

Humectants

Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel based nasal products to avoid nasal irritation and are not likely to affect drug absorption. Some common humectants used include glycerin, sorbitol and mannitol.

Absorption Enhancers

When it becomes difficult for a nasal product to achieve its required absorption profile, the use of absorption enhancers is recommended. The selection of absorption enhancers is based upon their acceptability by regulatory agencies and their impact on the physiological functioning of the nose. Absorption enhancers may be required when a drug exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation. Once a suitable enhancer is identified, its optimal concentration should be experimentally determined. Generally higher concentrations of enhancers are likely to result in nasal irritation and damage to the nasal mucosa. On the other hand, lower enhancer concentrations would generally provide lower or no improvement of absorption

ADVANTAGES [40] :-

- The nasal epithelium is thin, porous (especially when compared to other epithelial surfaces) and highly vascularised. This ensures high degree of absorption and rapid transport of absorbed substances into the systemic circulation for initiation of therapeutic action.
- A porous endothelial basement membrane that poses no restriction to transporting the drug into general circulation.

- Absorbed substances are transported directly into the systemic circulation thereby avoiding the first pass metabolic effect generally experienced following oral drug administration.
- In some cases, drugs can be absorbed directly into the CNS after nasal administration bypassing the tight blood brain barrier.
- Generally, the enzymatic activity of the nasal epithelium is lower than that of the GIT or liver and higher bioavailability of drugs especially proteins and peptides can be achieved. In addition, enzyme inhibitors are more effective following nasal than oral application because of a higher degree of dilution in the latter than in the former.
- Realization of pulsatile delivery of some drugs like human growth hormone, insulin, etc. is higher with NDD.
- The nose is amenable to self-medication that not only lowers the cost of therapy but improves patient compliance as well. The risk of Overdosage is low and nasal lavage can be used to remove unabsorbed excess drug.
- Reformulation of existing drugs as NDD products offers companies the possibility to extend the life cycle of their products.

DISADVANTAGES [41-45] :-

- Mucocilliary clearance reduces the residence time of drug.
- Not applicable to all drugs.
- Insufficient absorption due to lack of adequate aqueous solubility.
- Require high volume of dose (25-200 ml) depending upon aqueous solubility of drug.
- Few drugs can cause nasal irritation.
- Few drugs may undergo metabolic degaradation in the nasal cavity.
- Less suitable for chronically administered Drugs.
- Drugs required sustained blood levels should not be considered for nasal drug delivery.

EVALUATION OF NASAL IN SITU GEL SYSTEM :-

In situ gels may be evaluated and characterized for the following parameters,

Clarity [33]

The clarity of formulated solution was determined by visual inspection under black and white background.

Texture Analysis [33]

The firmness, consistency and cohesiveness of formulation are assessed using texture analyzer which mainly indicates the syringe ability of sol so the formulation can be easily administered in vivo.

Gelation Point [33]

It is temperature at which the liquid phase makes a transition to gel. A gelation temperature range suitable for thermoreversible nasal gel would be would be 30- 36°C. Gelation point was considered as the temperature where formulations would not flow when test tubes were tilted to 90° angle as the temperature was gradually increased. While in case of pH & ion dependant polymer there is change in pH or contact with nasal fluid they get change from sol to gel.

pH of the Gels [34]

The pH of each batch was measured using pH meter which was calibrated using buffers of pH 4 and pH 8 before the measurements.

Content Uniformity [34]

Weighed amount of the formulation was dissolved in medium and after suitable dilution the absorbance was measured using UV/visible spectrophotometer. The amount of the drug present in the formulation was calculated by measuring the absorbance of a standard solution of known concentration of drug prepared in distilled water.

Rheological Studies [34]

Viscosity of the prepared formulations was measured by using Brookfield Viscometer. The gel under study was placed in the small sample holder and the spindle was lowered perpendicularly into it. The spindle was rotated at varying speeds and the suitable speed was selected.

Gel Strength [33]

This parameter can be evaluated using a Rheometer. Depending on the mechanism of the gelling of gelling agent used, a specified amount of gel is prepared in a beaker from the sol form. This gel containing beaker is raised at a certain rate so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface.

Measurement of Gel Strength [33]

Formulated gels were placed in the test tubes and gelled in a thermostat at 37°C. The apparatus for measuring gel strength was then placed onto the in situ gel. The time taken by the apparatus to sink to a depth of 5 cm through the prepared gel was measured for each formulation. Weights that detached the two vials using the following equation,Detachment stress (dynes /cm2) = mg /A where m is the weight added to balance in grams, g is the acceleration due to gravity taken as 980 cm/sec2, A is the area of the tissue exposed and is equal to πr2 (r is the radius of the circular hole in the aluminium cap).

In vitro Nasal Diffusion Cell [34]

The nasal diffusion cell was fabricated in glass. Drug release from gel was tested with nasal diffusion cell using dialysis membrane (mol.wt.12, 000-14,000 kDa) with permeation area of 0.785 cm2. 20ml of diffusion medium was added to the acceptor chamber. Gel containing drug equivalent to its dose was placed in donor compartment. At predetermined time points, 1ml sample was withdrawn from the acceptor compartment replacing the sampled volume with diffusion medium after each sampling. The samples were suitably diluted and measured spectrophotometrically. The concentration of drug was determined from a previously constructed calibration curve.

Fourier Transform Infrared Spectroscopy and Thermal Analysis [34]

During gelation process the nature of interacting forces can be evaluated using this technique by employing KBr pellet method. Thermogravimetric analysis can be conducted for in situ forming polymeric systems to quantitate the percentage of water in hydrogel. DSC is used to observe if there are any changes in thermograms as compared with the pure ingredients used thus indicating the interactions.

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