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REVIEW: NASAL DRUG DELIVERY

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ABSTRACT
The nasal drug delivery used for local, systematic and also for bypass brain targeting in present sinariorio. These deliveries have various advantage of high bioavability, sustained release due to mucoadhesion this give long residesion time, rapid absortion due to rich vasculature and highly permeable structure of nasal mucosa. Various promising pharmaceutical formulation have been used such as suspension, powders, emulsions, ointments, microsphere, liposomse and proliposomes. In this presented article, intra-nasal physiology and anatomy , mechanism of the drug absorption from nasal mucosa along with various factor that affect on absorption of the drug related to drug, formulation and nasal patho-physiology are discussed.

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INTRODUCTION

Drugs have been administered nasally for therapeutic and recreational purposes since ancient times. Psychotrophic drugs and halucinogens were snuffed for their purposes by the Indians of South America, and this practice is currently widespread among abusers of cocaine and heroin. Traditionally the nasal route has been used for delivery of drugs for local treatment of diseases such as nasal congestion, allergy and infections. The interest in and importance of the systemic effect of drugs administered via the nasal route have expanded over recent decades[1]. Nasal administration offers an interesting alternative for achieving systemic drug effects to the parenteral route, which can be inconvenient, as parental route can be undesirable or impractical if a drug is intended for the treatment of chronic disease or oral administration, which can result in unacceptably low bioavailabilties because of significant degradation in the GIT due to enzymatic or acidic environment or metabolized to a high degree via the first pass effect in the liver[2]. The non parenteral routes suitable for self administration of drug in ambulatory setting includes nasal, buccal, pulmonary and transdermal. The nasal epithelium is a highly permeable monolayer, the submucosa is richly vascularised and hepatic first pass

metabolism is avoided after nasal administration. Other attractive feature includes the rather large surface area (180 cm^2 because of the presence of large no. of microvilli) of the nasal cavity and the relatively high blood flow, which promotes rapid absorption, porous endothelial membrane and highly vascularised tissue providing an attractive site for rapid and efficient systemic absorption, furthermore, self medication is easy and convenient[3]. Currently, nasal administration is used therapeutically for the systemic absorption of drugs in a variety of indications, including sumatriptan for migraine[7], the antidiuretic desmopressin for the treatment of diabetes insipidus[8] and oxytocin for the stimulation of breastmilk ejection[4]. Other drugs still in the researh and development pipeline, which have potential for administration nasally includes vitamin B12 or hydroxocobalamine, various benzodiazepines and the dopamine agonist apomorphine for patients with parkinsonism[5].

Overview of Nasal Mucosa

Anatomy and Function

Breathing and olfaction are the prime functions of the nasal cavity in humans and animals. Physiologically, the structure and function of this cavity are also related to the resonance of produced sounds, the filtration of particles, mucociliary clearance, immunological activities, and heating and humidification of the inspired air before it reaches the lungs[1]. The nasal passage which runs from nasal vestibule (i.e. nasal valve) to the nasopharynx has a depth of approximately 12-14 cm. The nasal septum divides the nasal cavity into two unequal cavities[2]. The septum consists mostly of cartilage and skin and therefore, the penetration of drug is low. The nasal cavity can anatomically be segregated into five different regions, nasal vestibule, atrium, respiratory area, olfactory region, and the nasopharynx as shown in **Figure 1**. The vestibular area serves as a baffle system, and its surface is covered by a common pseudo stratified epithelium where long hair may provide the function of filtering airborne particles. Secondly the olfactory region which is located on the roof of the nasal cavity in humans and forms about 10% of the total area of nasal cavity. Thirdly respiratory region consists of the inferior, middle and superior turbinate attached to the lateral wall, and is considered as major site of drug absorption into the systemic circulation[3]. The respiratory area has a surface lined by a pseudo stratified columnar epithelium and is normally covered by a dense layer of mucus[11]. These cells are covered by microvilli and the major part of these cells is also covered with cilia. Large number of microvilli results in increased surface area of 180 cm^2 responsible for relatively high absorptive capacity of the nasal cavity, whereas ciliated cells propel the mucus layer in a direction from the anterior towards the posterior part of the nasal cavity. Cilia beat with a frequency of 1000 strokes per minute and the mucus is transported at the rate of 5 mm per minute. The mucus layer is renewed every 15-20 min and hence the formulations applied to human nasal cavity are cleared with a clearance half-life of 15 minutes[12, 13].

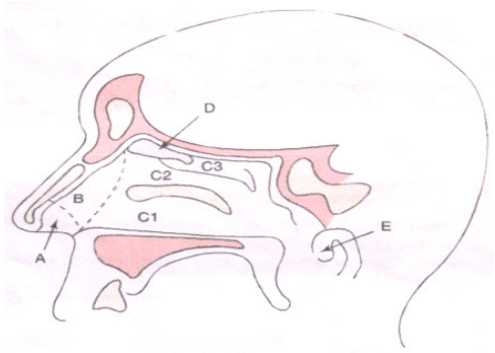

Figure 1: Saggital section of the human nasal cavity, showing the nasal vestibule (A), Atrium (B), Respiratory Area: Inferior (C1), Middle (C2) and Superior (C3) turbinate, Olfactory region (D) and Nasopharynx (E) [8].

Nasal Epithelium

The nasal cavity is highly vascularised and its membrane can be classified into two types: olfactory and non-olfactory. The olfactory epithelium is a pseudo stratified columnar structure. It consists of specialized olfactory cells, supporting cells, serous and mucosal glands. The nonolfactory part is a vascular membrane. Its surface is covered by ciliated pseudo stratified columnar epithelium. Numerous groups of microvilli can be seen microscopically among the group of cilia. All microvilli are of short club like appearances and there are approximately 500 microvilli on the surface of each ciliated cell. These cells with microvilli are called goblet cells. Another type of epithelial cells are observed in the free surface of the mucous membrane. They are rounded or elongated in shape and rough on the surface. These cells are defined as squamous cells.

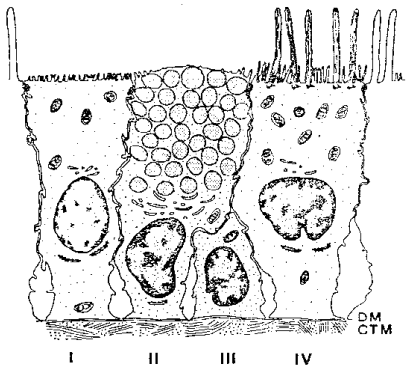

Figure 2: Trans-membrane electron microscopic view of various cell types in the nasal epithelium.

Nasal Secretions

The composition of the nasal secretions is complex and consists of a mixture of secretary materials from the goblet cells, nasal glands, and lacrimal glands and a transudate from plasma. In a clean, noninfected, nonallergic, and nonirritated nose, the mucosa is covered by a thin layer of clear mucus which is secreted from the mucous and serous glands in the nasal mucosa and sub mucosa. A total of approximately 1500-2000 ml of mucus is produced daily, which contains 90-95 % water, 1-2 % salt and 2-3 % mucin. The mucus has a two-layer composition: The watery (sol) layer is located immediately adjacent to the mucosal surface, and the mucous (gel) layer, which is more superficial. Normal Nasal secretions contain about 150 mEq/L of sodium, 40 mEq/L of potassium, and 8mEq/L of calcium as well as about 600 mg % of proteins, including 57 mg % of albumins and 133 and 50 mg % of immunoglobulin A (IgA) and G (IgG) respectively. In addition to mucous glycoproteins, nasal secretions contain a variety of other proteins, lysozymes, enzymes, Ig A, Ig E, Ig G and albumins, kallikrein like substances, protease inhibitor, prostaglandins, as well as serum proteins like gamma A-globulin, gammaG -globulin, albumin and siderophilin.

Nasal Mucociliary Clearance

Nasal mucociliary clearance is normal defence mechanism of the nasal cavity that clears mucus as well as substances adhering to the nasal mucosa (bacteria, allergens, and so on) and drains them into the nasopharyx for eventual discharge into the gastrointestinal tract. There are approximately five ciliated cells for each mucous cell, with an average of 200 cilia extending from every ciliated cell on the surface of pseudo stratified columnar epithelium. An individual cilium is approximately 5 µm in length and 0.2 µ in diameters, which moves at a frequency of about 20 beats/sec. nasal clearance proceeds at an average rate of about 5-6 mm/min. Normal mucociliary transit time in humans has been reported to be 12-15 min. Transit times more than 30 min are considered to be abnormal, and are indicative of impaired mucociliary clearance. Formulations administered to the human respiratory epithelium have been found to be cleared from the nasal cavity in ~ 21 min by mucociliary clearance.

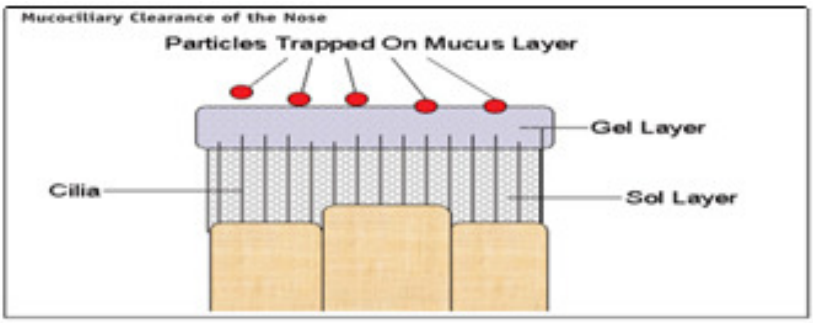

Figure 3: Mucocilliary clearance of the nose

Nasal Enzymes

Nasal mucus acts as enzymatic barriers to the delivery of drugs because of the presence of a large number of enzymes. They are cytochrome P-450 dependent monoxygenases, Lactate dehydrogenase, oxydoreductases, hydrolases acid phosphatase and esterase, NAD^+ dependent formaldehyde dehydrogenases and aldehyde dehydrogenase; leucine amino peptidase, phosphoglucomutase, glucose-6-phosphate dehydrogenase, aldolase, lactate dehydrogenase, isocitric dehydrogenase, glutamic pyruvic transaminase and steroid hydroxylases. These enzymes are responsible for the degradation of drugs in the nasal mucosa and results in creation of a pseudo-first pass effect, which hampers the absorption of drugs[8]. The level of amino-peptidase present is much lower than that in the gastrointestinal tract. Various approaches have been used to overcome these degradations. These include the use of protease and peptidase inhibitors such as bacitracin, amastatin etc. Apart from using enzyme inhibitors, efforts are focused on designing prodrug to increase the stability and permeation of compounds. Although enzymes are known to exist in the nasal tissues, they do not appear to have a significant effect on the extent of absorption of most compounds except peptides. For example, the nasal bioavailability in animal and man of progesterone, testosterone, estradiol, naloxone, propranolol and butorphanol .These low oral bioavailabilities are due to the extensive metabolism of the compounds in the gastrointestinal tract. The nasal administration of these compounds results in complete absorption because the level of the enzymes in the nasal tissue (mg/g) is very low and can be easily saturated with the drug[15].

Nasal pH

The normal pH of the nasal secretions in the adult ranges approximately from 5.5 to 6.5, whereas in infants and young children it ranges from 5.0 to 6.7. During acute rhinitis, acute sinusitis, and in the more acute phases of allergic rhinitis, the pH of the nasal secretions was found to be on the alkaline side and then shifted back to acidity, when the stage of clinical resolution was reached. The cause of nasal pH can be altered by the influence of cold or heat. Cold air produces a drift towards alkalinity, whereas heat yields a drift toward acidity. Greater drug permeation is usually achieved at a nasal pH that is lower than the drugs pKa because under such conditions the penetrate molecules exist as unionized species. Because the pH of the nasal cavity can alter the pH of the formulation and vice-versa, the ideal pH of a formulation should be within 4.5-6.5[11].

Nasal Blood Flow

The nasal mucosa is highly vascular. The surface of epithelium is supplied with a dense network of erectile cavernous tissue which is particularly well developed over the turbinate and septum. The presence of venous sinusoids and arteriovenous anastomosis gives the nasal mucosa the distinction of being a highly permeable site. The arterial blood supply to the nasal cavity is derived from both the external and internal carotid arteries. The terminal branch of the maxillary artery supplies the sphenopalatine artery which in turn supplies the lateral and medial wall of the nasal chamber. The anterior and posterior ethmoid branches come from the ophthalmic artery, which is a branch of

the carotid artery. These vessels supply the anterior portion of the nose. Additionally, twigs from the facial artery supply the vestibule and anterior portion of the septum. Some vessels from the greater palatine artery pass through the incisive canal of the palate to reach the anterior part of the nose. The veins of the nasal cavity drain into the sphenopalatine foramen and then into the pterygoid plexus. Some other veins accompany the ethmoid arteries and join the superior ophthalmic vein. Veins which are anterior in the nose drain into the facial vein. The richly supplied vascular nature of the nasal mucosa, coupled with its low barrier to drug permeation, makes the nasal route of administration attractive for a number of drugs, both peptide and nonpeptide drugs. In addition, the olfactory region provides a potential advantage whereby a drug may be exposed to neurons that may facilate its access into the cerebral spinal fluid, when administered nasally. Constriction of the blood vessels would decrease blood flow and blood content in the nasal mucosa, whereas vasodilation would yield the opposite response. The penetration of the drug through the sinus mucosa is partly influenced by the blood flow in the region under normal and pathological conditions[11].

Nasal Pathophysiology

Diseases such as the common cold, rhinitis, atropic rhinitis, nasal polyposis are usually associated with mucociliary dysfunction, hypo and hyper secretions, and irritation of the nasal mucosa, which can influence drug permeation and subsequently, the therapeutic efficacy of the drugs administered nasally. In some subjects with a severe nasal allergy, an excessive response of the secretary system to irritants could wash away the drug solution administered into the nasal cavity before the drug is absorbed by the nasal membrane[1].

Tight Junctions (TJ)

TJs are structure that form a barrier between adjacent epithelial cells with a narrow band just beneath the apical surface, and are found in all tissues of the body. They perform two vital functions: as a barrier or gate to the movement of molecule between cells in the paracellular space, and as a fence to prevent diffusion of integral membrane proteins between the apical and basolateral surfaces, thus preserving, for example, the special function of receptor mediated endocytosis at the apical surface and exocytosis at the basolateral surface[9]. High molecular weight drugs need to pass through TJ barriers in order to become systemically available and to move to their site of action as part of the bodies normal activity, TJs selectively modulate paracellular permeability by opening and closing in response to various signals inside and outside of cells, including responding to cytokines, immune cells, nutrients, calcium depletion and lipid modifying agents. TJs consist of a variety of integral membrane and peripheral, or associated, proteins, which are anchored in the membranes of two adjacent cells and interact across the paracellular space by noncovalent forces .In the cytoplasm, TJ membrane proteins interact with scaffold proteins to connect them with the cellular cytoskeleton and various signal transduction and transcriptional pathways involved in the regulation of TJ function. Dysregulation of TJ function occurs in a variety of diseases, particularly inflammation, cancer and CNS pathologies where normal tissue permeability and cell adhesion interactions are altered[17].

Transmembrane Proteins of the Junctional Complex

Epithelial cells characteristics of the nasal mucosa, like other tissues, are joined together by TJs. The closely associated adherens junction is found on the basolateral side but is not circumferentially continuous, like the TJ, and therefore does not contribute significantly to the epithelial barrier properties. The cell membranes of adjacent cells are intimately connected by proteins of the junctional complexes to an extent that one can measure a significant transepithelial electrical resistance (TEER). Freeze fracture electron microscopy (but not thin sections) visualises TJs as a network of strands that appear as rows of 10 nm particles within the plane of the plasma membranes of the neighbouring cells. These strands have been predicted to contain pores that dynamically open and close. Three major types of

integral proteins comprise TJs: Occludin, claudins and junction adhesion molecules (JAM) These junctional proteins are involved in cell-cell adhesion and are dynamically regulated .A group of scaffolding proteins, including a family of zonula occludens (ZO) proteins, connect TJs and AJs to the cytoskeleton and mediate intracellular signaling. A number of additional cytosolic and nuclear proteins interact directly or indirectly with TJ scaffolding proteins and are also involved in regulating diverse functions including paracellular permeability cell polarity etc claudins may be the single most important component of the TJ because they alone can form TJ strands. Claudins play a key role in regulating ion flux as major components of paracellular channels,where indivisual claudins function as ion–specific pores. E-cadherin is a 120-k Da a transmembrane protein, which is a constituent of the AJ. It is important for initiating and maintaining cell-cell contacts and is required for the formation of and maintenance of TJs. Chitosan has been shown to disrupt intercellular TJs, thus increasing permeability by translocation of TJ proteins from the membrane to the cytoskeleton. Immuno fluorescent localization of ZO-1 revealed loss of membrane associated ZO-1 and occludin from the cytosolic and membrane fractions into the cytoskeletal fraction[18].

Drug Absorption through the Nasal Mucosa

The first in the absorption of drugs from the nasal cavity is passage through the mucus. Small uncharged particles easily pass through this layer. However larger particles may find it more difficult to cross. Mucin the principle protein in the mucus has the potential to bind solutes, hindering diffusion. Additionally structural changes in the mucus layer are possible as a result of environmental changes, (i.e. pH and temperature). After a drug passage through the mucus, there are several mechanisms for absorption through the mucosa.

Mechanism of Drug Absorption

As seen with the other epithelium in the body, absorption across nasal epithelium can occur by one or combination of mechanisms. Following two mechanisms have been considered predominantly. The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. Drugs are believed to pass through the epithelium via the gaps or pores between the cells (the tight junction). This route is slow and passive and this pathway is especially suited for smaller hydrophilic molecules. Although, the tight junctions are dynamic structures that can open and close to certain extent, the size of these channels is less than 10 A^{o}. There is an inverse log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Hence, the paracellular route will be less efficient for large molecules and is dependent upon the molecular weight of the drug with a general molecular size cut – off of 1000 Dalton. 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 by an efficient concentration dependent passive diffusion process, by receptor or carrier mediation and by vesicular transport mechanism. This pathway is especially suited for small lipophilic molecules or large molecules[12].

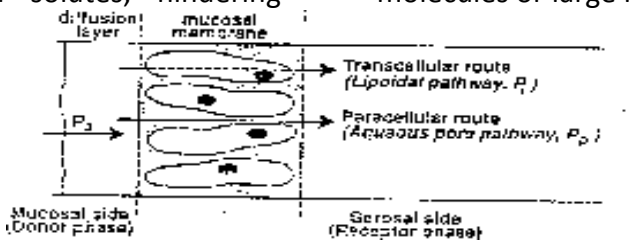

Figure 5: Diagram showing the physical model for transmembrane permeation across a mucosal membrane

Intracellular axonal transport of drugs through olfactory neuron cells is also one of the mechanisms, responsible for transport of drugs primarily to the olfactory bulb. The olfactory epithelium is known to be a portal of entry for substances into the central nervous system (CNS) and peripheral circulation. The transport of drugs across the nasal membrane and into the blood

stream may involve either passive diffusion of the drug molecules through the pores in the nasal mucosa or some form of non-passive transport. The can enter into the CNS when administered in the nasal cavity, a proportion is transported through the olfactory lobes of the brain, or in some cases, further into the parenchyma of the brain. It has been show that the rate and degree of transport and deposition are highly dependent on the physicochemical properties of the drugs, especially molecular weight and the lipophilicity. When drugs are administered nasally the drug will normally be rapidly cleared by the mucocilliary mechanism. Some of the drug will be absorbed into the blood stream from where it reaches the systemic circulation directly and subsequently is eliminated from the blood by crossing the blood brain barrier, but can also be eliminated from CSF into the brain[19].

Factors influencing the absorption of drugs through nasal epithelium

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

Biological

A) Structural features
B) Biochemical changes
C) Physiological factors

- Blood flow
- Nasal secretions
- pH of the nasal cavity
- Mucocilliary clearance and ciliary beat frequency

D) Pathological conditions
E) Environmental factors

- Temperature
- Humidity

II. Device related

- Particle size of the droplet/powder
- Size and pattern of disposion[8]

Physiological factors include firstly mucociliary clearance is one of the major factor responsible for the clearance of the drugs from the nasal cavity, 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. 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[16].

Physicochemical characteristics 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[12].

Solubility and Dissolution:

Drug solubility is a major factor in determining absorption of drug through biological membranes. It not only limits the drug absorption per se, 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[12].

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[12].

Partition Coefficient and pKa

Jiang *et al.* (1997) conducted a study to find out the quantitative relationship between the physiochemical properties of drugs and their nasal absorption, using diltiazem hydrochloride and paracetamol as model drugs. The result showed that a quantitative relationship existed between the partition coefficient and nasal absorption 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. A relationship between the lipophilicity and absorption rate constant of mucosal absorption of progesterone was shown by Corbo *et. al*. 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. The nasal absorption of weak electrolytes such as salicylic acid and aminopyrine was found to be highly dependent on their degree of ionization. Although for aminopyrine, the absorption rate increased with the increase in pH and was found to fit well to the theoretical profile, substantial deviations were observed with salicylic acid. The authors concluded that perhaps a different transport pathway, along with the lipoidal pathway, existed for salicylic acid. Similarly when the absorption of benzoic acid was studied at PH 7.19 (99.9 % of the drug existed in ionized form) it was found that >10 % of drug was absorbed indicating that the ionized species also permeates through nasal mucosa. Based on all of these observations, the authors discounted partition coefficients as a major factor governing nasal absorption and supported that other transport pathways for hydrophilic drugs might be of importance[12].

Factors Related to 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. However, in another study, aminopyrine was found to absorb at a constant rate as a function of concentration. Several studies have reported the effect of drug 'dose' on nasal absorption,e.g. calcitonin, GnRH agonist, desmopressin, secretin. 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[16].

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. Harris et al. studied the nasal delivery of desmopressin and reported that although the addition of the viscous agents to nasal formulations 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. One may also consider developing gel type formulations for those drugs, which cause unpleasant taste in the mouth via a nasal drip of solution or spray formulations. Nasal drip would be minimized from viscous formulations[16].

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.

Lysozymes are found in nasal secretions, which is 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 keeping in mind the physicochemical properties of the drug as drugs are absorbed in the unionized form and also to avoid nasal irritation[16].

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 un-ionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH *in situ*[16].

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[8].

Gelling Agents or Gel Forming Carriers

Some formulations need to be gelled or made more viscous to increase nasal residence time. According to a study by Pennington *et al.* increasing the solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations. Suzuki et al. showed that a drug carrier such as hydroxypropyl cellulose 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[16].

Solubilises

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, (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol (saturated polyglycolyzed C_8-C_{10} glycerides) 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[16].

Preservatives

Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations. Preservatives are based in small quantities and are not likely to affect drug absorption[16].

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 hydroxytoluene and to copherol. Usually, antioxidants are used in small quantities and they may not affect drug absorption or cause any nasal irritation. Chemical/physical interactions of antioxidants and preservatives with drugs, excipients, manufacturing equipment and packaging components should be considered as a part of formulation development program[16].

Humectants

Many allergic and chronic diseases are often connected with crusts and drying of mucous membranes. Certain preservatives/antioxidants among the other excipients are also likely to cause nasal irritation especially when used in higher quantities. Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel-based nasal products. Humectants avoid nasal irritation and are not likely to affect drug absorption. Some common humectants used include glycerin, sorbitol and mannitol[17].

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 by aminopeptidases. 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[1].

Mechanism of Nasal Drug Absorption Enhancers

The enhancers evaluated to date appear to act by a wide range of mechanisms, including perturbation of lipid membranes, facilitation of leakage of lipids and proteins from the membranes, tight junction regulation, and chelation of Ca2+ ions in the cell membranes. Precise mechanisms of enhancer effect are not known. However, it is generally believed that enhancers may show their actions via one or both of the following mechanisms:

Physicochemical Effects

Some enhancers can alter the physicochemical properties of a drug in the formulation. This can happen by altering the drug solubility, drug partition coefficient, or by weak ionic interactions with the drug. This mechanism of drug absorption enhancement is desirable because it can be effective with the lowest potential of toxicity.

Membrane Effects

Many enhancers show their effects by affecting the nasal mucosal surface. It should be emphasized that these effects are not necessarily harmful. In most cases the enhancer's effects are transient with no lasting or pathological consequences. The final decision should take into consideration the benefit to risk ratio. Generally, the absorption enhancers act via one of the following mechanism.

- Inhibit enzyme activity
- Reduce mucus viscosity or elasticity
- Decrease mucociliary clearance
- Open tight junctions
- Solubilize or stabilize the drug[21]

Nasal Formulations

Several new preparations mentioned below have been developed for nasal route not only to prolong the contact time of the vehicle on the nasal mucosal surface but also to slow down the drug clearance unlike nasal drops

Suspension[8]

Powders[31]

Emulsions and ointments[32]

Microsphere[27,33,34]

Liposomse and Proliposomes[35,36]

Mucoadhesive drug delivery system[37,37,39]

CONCLUSION

Nasal delivery is a feasible alternative to oral or parenteral administration for some drugs because of the high permeability of the nasal epithelium rapid drug absorption across this membrane and avoidance of hepatic first pass metabolism. The nasal dosage form includes solution, sprays, microspheres, gels and liposomes. Although solutions are easy to use they achieve a poor bioavailability, due to large mucocilliary clearance. It had been demonstrated that a significant improvement in bioavailability would be achieved if the nasal residence time of the drug would be increased. From the point of view of patient acceptability a liquid dosage form that can be

administered easily and can adhere to the nasal mucosa for extended period with fast onset of action is ideal.

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