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A Review Based on Nasal Drug Delivery System

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A B S T R A C T

Nasal drug delivery system (NDDS) has been used as a substitute route for the systemic accessibility of drugs restricted to intravenous administration. This is due to the porous endothelial membrane, large surface area, high total blood flow, the avoidance of first-pass metabolism, and ready accessibility. The nasal administration of drugs, including various compound, peptide and protein drugs, for systemic medication has been widely investigated in recent years. Drugs are cleared rapidly from the nasal cavity after intranasal administration, resulting in rapid systemic drug absorption. Several approaches are here discussed for increasing the residence time of drug formulations in the nasal cavity, resulting in improved nasal drug absorption. The article highlights the importance and advantages of the drug delivery systems applied via the nasal route, which have bioadhesive properties. Bioadhesive or more appropriately, mucoadhesive systems have been prepared for both oral and peroral administration in the past. The nasal mucosa presents an ideal site for bioadhesive drug delivery systems.

Keywords: NDDS, Drug administration, systemic medication

A R T I C L E I N F O

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1. Introduction

The history of nasal drug delivery dates back to earlier topical applications of drugs intended for local effects. Nasal therapy also called 'Nasya karma' has been recognized form of treatment in the Ayurvedic system of

Indian medicines [1]. The early 1980s saw the introduction of nasal route as a promising systemic delivery alternative to other conventional drug delivery routes [2]. Nasal route is easily accessible, convenient, and a reliable 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 [3, 4].

The low metabolic environment of nose has potential to overcome the limitation of oral route and duplicate the benefit of intravenous administration. In addition to that, nasal administration minimizes the lag time associated with oral drug delivery and offers noninvasiveness, self-administration, patient comfort, and patient compliance, which are the hurdles in intravenous drug therapy. [5] It was reported that lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profiles, which are often identical to those obtained after an intravenous injection with a bioavailability approaching 100% [1], on the other hand absorption of hydrophilic drugs can be increased by means of absorption enhancers. [2]

Drugs ranging from small chemicals to large macromolecules including peptide/protein therapeutics, hormones, and vaccines, are being delivered through the nasal cavity [6]. The nasal delivery seems to be a favorable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS) active compounds. It has also been considered to the administration of vaccines [7-8]. Buserelin, desmopressin, calcitonin, insulin luteinizing hormone releasing hormone, growth hormone and adreno-corticotrophic hormone are some of the peptides that have been successfully administered through the nasal route. Apart from these, steroids (corticosteroids, estradiol, progesterone, testosterone, and so on) [9, 10]

Antihypertensive (nifedipine, nitroglycerine, propranolol, hydralazine, and so on), analgesics (buprenorphine), antibiotics and antivirals [11] have been shown to produce considerable systemic effects when administered via the nasal cavity. For nasal drug delivery various systems such as: nasal spray, nasal pumps, gels, microemulsion, suspensions, powders and thermo reversible mucoadhesive gels have been studied [12]. During the past several decades, the feasibility of drug delivery via the nasal route has received increasing attention from pharmaceutical scientists and clinicians.

Advantages of nasal drug delivery system [13, 14, 15]

- Absorption of drug is rapid via highly vascularised mucosa.
- Availability of large nasal mucosal surface area for dose absorption.
- Onset of action is rapid.
- Noninvasive and easy for administration.
- Bypass the Blood Brain Barrier.
- Degradation of drug observed in GIT is avoided.
- Hepatic first pass metabolism is absent.
- Nasal bioavailability of small drug molecules is good.
- Bioavailability of large drug molecules can be increased by means of absorption enhancers.
- Unsuitable drug candidates for oral route can be successfully given via nasal route.
- Alternate to parenteral route especially for proteins and peptides.
- Convenient route for the patient on long term therapy.
- Improved bioavailability.
- Side effects are reduced due to low dose.
- Patient convenience and compliance is improved.
- A self-administration is possible.
- Direct transport into systemic circulation and CNS is Possible.
- Offers lower risk of overdose
- Does not have any complex formulation requirement

2. Limitations of nasal drug delivery system

- Delivery volume in nasal cavity is restricted to 25–200 μL.
- High molecular weight compounds cannot bedelivered through this route (mass cut off ~1kDa).
- Adversely affected by pathological conditions.
- Large interspecies variability is observed in this route.
- Normal defense mechanisms like mucociliary Clearance and ciliary beating affects the permeability of drug.
- Irritation of nasal mucosa by drugs like Budesonide, Azilactine.
- Limited understanding of mechanisms and less developed models at this stage.
- Systemic toxicity occurring due to absorption enhancers is yet not established.
- Smaller absorption surface compared with GIT.
- Possibility of nasal irritation hence inconvenient compared with oral route.
- Enzymatic barrier to permeability of drug.

Profile of an 'ideal' drug candidate for nasal delivery

An ideal nasal drug candidate should possess the following attributes: [16]

- Appropriate aqueous solubility to provide the desired dose in a 25–150 ml volume of formulation administration per nostril.
- Appropriate nasal absorption properties.
- No nasal irritation from the drug.
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
- Low dose. Generally, below 25 mg per dose.
- No toxic nasal metabolites.
- No offensive odors/aroma associated with the drug.

- Suitable stability characteristics.

Anatomy and physiology of nasal cavity

Researchers became interested in the nasal route for the systemic delivery of medication due to a high degree of vascularization and permeability of the nasal mucosa [17]. In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. However, it also affords an important protective activity once it filters, heat and humidify the inhaled air before reaching the lowest airways. Passage of the nasal cavity which runs from nasal vestibule to nasopharynx has a depth of approximately 12-14cm. The total surface area of the nasal cavity in human adult is about 150 cm2 and total volume is about 15 ml [18]. Each of two nasal cavities can be subdivided into different regions: nasal vestibule, inferior turbinate, middle turbinate, superior turbinate, olfactory region, frontal sinus, sphenoidal sinus, and cribriform plate of ethmoid bone.

The nasal cavity also contains the nasal associated lymphoid tissue, which is mainly situated in the nasopharynx. Nasal cavity is lined with mucus layer and hairs which are involved in those functions are trapping inhaled particles and pathogens. Moreover, mucociliary clearance, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures [19]. The nasal cavity is covered with a mucous membrane which can be divided into two areas; nonolfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, whereas respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport [20] . Nasal cavity is divided by middle septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics [19]

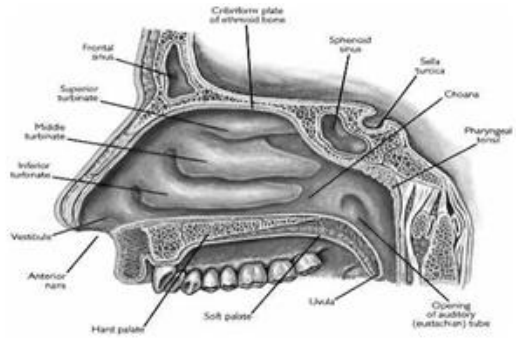

Figure 1

Nasal vestibule

Most anterior part of the nasal cavity is nasal vestibule, just inside the nostrils, and presents an area about 0.6 cm2 [4]. Nasal hairs are present in this area, also called vibrissae, which filter the inhaled particles. Histologically, this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands.

Atrium: Intermediate area between nasal vestibule and respiratory region is atrium. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by psudostratified columnar cells presenting microvilli [21, 22].

Respiratory region

Largest part of the nasal cavity is respiratory region, also called conchae, is the cavity and it is divided in superior, middle and inferior turbinates which are projected from the lateral wall. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. The nasal respiratory epithelium consists of pseudostratified columnar epithelial cells, globet cells, basal cells and mucous and serous glands [8]. Many of the epithelial cells are covered on their apical surface with microvilli and the major part of them also has fine projections, called cilia.

Olfactory region

Location of olfactory region is at the roof of the nasal cavity and extends a short way down the septum and lateral wall. Its neuro-epithelium is the only part of the CNS that is directly exposed to theexternal environment. Similarly to the respiratory epithelium, the olfactory one is also pseudostratified but contains specialized olfactory receptor cells important for smell perception [21,22].

Mucus membrane of nose and its composition

The nasal mucus layer is only 5 μm thick and it is organized in two distinct layers: an external, viscous and dense, and an internal, fluid and serous. Overall, nasal mucus layer consists of 95% of water, 2.5-3% of mucin and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products.

Epithelial cells

Basically there are two functions of these cells, **which are**

1. Provide a physical barrier to the invasion of infectious microorganisms and allergic particles;
2. Work in conjunction with mucus glands and cilia to secrete and remove mucus and foreign particles from the nasal cavity [23].

Blood supply to nasal cavity

Vasculature of the nasal cavity is richly supplied with blood to fulfill the basic functions such as heating and humidification, olfaction, mucociliary clearance and immunological functions. The nasal vascular bed is so designed that rapid exchange of fluid and dissolved excipients between blood vessels and nasal tissue can be done easily. The capillary flow in the nasal mucosa was reported to be 0.5 ml/g/min [14].

- Sphenopalatine arterya branch of maxillary artery.
- Anterior ethmoidal arterya branch of ophthalmic artery.
- Branches of the facial artery supplyingthe vestibule of the nasal cavity.
- Mechanism of drug absorption from nose

3. Factors affecting nasal drug absorption

Various factors affect bioavailability of nasally administered drugs as follows; **[4, 14,]**

I Biological Factors [4]

- 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 [4]

- 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

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. [25]

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 [26].

II Physiological factors

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 [27]. Based on the above observations, we can conclude that the increased permeability of a compound is due to parasympathetic stimulation.

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 clearance rates are reduced. Chronokinetics dictate the pattern and rate of permeation in such cases.

pH of nasal cavity [28]**:**

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 such conditions 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.

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.

Pathological conditions: Mucociliary disfunctioning, hypo or hyper secretions, 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.

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.

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 [29].

III Physicochemical properties of drug:

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.

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. [30]

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.

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 [31].

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 development for the nasal delivery. [16]

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

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. [16].

VI Physicochemical properties of formulation:

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.

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.

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 sodium chloride 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. [32]

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. [33]

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

Strategies to improve nasal absorption [34]

There are many barriers present in nasal cavity which interfere with absorption of various drugs. There are some methods which have been successfully used for the improvement of nasal drug absorption.

Nasal enzymes inhibitors: Various kinds of enzyme inhibitors are utilized to minimize metabolism of drug in nasal cavity which minimize activity of enzymes present in nasal cavity includes protease and peptidase, used as inhibitors for the formulation of peptide and protein molecule.

Structural modification: Modification of drug structure can be done without changing the pharmacological activity for improvement of nasal absorption.

Permeation enhancer:

Permeation enhancers are of different categories and have been investigated to improve the nasal absorption like surfactants, fatty acids, phospholipids, cyclodextrins, bile salts, etc.

Particulate drug delivery:

Carriers are used for the encapsulation of drug which prevent exposure of a drug to nasal environment and improve the retention capacity in nasal cavity. Some examples of carriers may include microspheres, liposomes, nanoparticles and niosomes.

Prodrug approach:

Inactive chemical moiety is called Prodrug which becomes active at the target site. Prodrugs are mainly used to improve taste, odor, solubility and stability.

Bioadhesive polymer:

To improve the nasal residence and absorption of the drug bioadhesive polymers are used. They improve the retention time of the drug inside the nasal cavity is increased by making an adhesive force between formulation and nasal mucosa, which leads to minimization of mucociliary clearance of formulation.

In situ gel:

These are the formulations which get converted into gel upon instillation into nasal cavity by the influence of stimuli includes temperature, pH and ionic concentration. Consistency of the gel is thick which makes the formulation difficult to drain by the influence of ciliate movement.

Physicochemical properties of drugs which affect their nasal delivery

Drug molecular weight and size: The permeation of drugs having molecular weight less than 300Da is not significantly influenced by the physicochemical properties of the drug as they will mostly permeate hrough aqueous channels of the membrane. On the other hand, the rate of permeation is highly sensitive to molecular weight for compounds more than 300 Da [35]. The bioavailability of intranasally administered peptides and proteins including insulin may be low because of high molecular weight and hydrophilicity [36].

Drug solubility and dissolution rate

Like other routes of administration, the nasal absorption can take place only after the drug's dissolution. The dissolution rate is important in determining nasal absorption of powder and suspensions dosage forms. Rapid dissolution is very crucial for the drug particles after nasal administration otherwise the particles will be subjected to rapid clearance from the airway with subsequent reduction of the bioavailability [37].

pKa and the partition coefficient of drug

The nasal membrane is predominantly lipophilic, hence, the rate and extent of absorption of a drug across a biological membrane is influenced by its lipophilicity. Normally, the permeation of the compound through nasal mucosa increases with increasing lipophilicity [38]. Low molecular weight lipophilic drugs are absorbed quite efficiently across the nasal epithelium, whereas larger hydrophilic drugs, such as peptides and proteins, have substantially lower bioavailability because they are not easily transported across nasal membrane thereby enhancing mucociliary clearance. However, if lipophilicity is too high, the drug does not dissolve easily in the aqueous environment of nasal cavity, hence, with accelerated mucociliary clearance the contact time with nasal membrane diminishes resulting in a reduced permeation through the wall [39]. In general, the passage across biomembrane is affected not only by lipophilicity/hydrophilicity, but also by the amount of drug existing as uncharged species. This depends on the drug pKa and the pH of the absorption site. According to pH partition theory, the non-ionized fraction of a drug is more permeable than that ionized. The nasal absorption of week electrolytes depends on their ionization degree and the largest absorption occurs for the non-ionized species. For polar drugs partition coefficient is the major factor influencing the permeability through nasal mucosa.

Chemical state: prodrugs

The chemical form in which a drug is presented at the nasal mucosa can be important in determining its absorption. If a drug does not have the desired absorption properties, several options can be considered to improve the drug's delivery. Prodrug technique has been employed to increase the lipophilicity. The aliphatic prodrug of acyclovir provides a classical example of this process, which resulted in an increased drug bioavailability. However, it should be noted that

the 140-fold increase in partition coefficient of the drug was only associated with 30% increase in bioavailability. It should also be emphasized that the ester form of the prodrug can showgreater increase in transnasal drug transport but premature hydrolysis of such ester in the nasal cavity provides the main limitation of this technique [40]. Water-soluble prodrugs of 17β-estradiol have been evaluated after intranasal administration. These prodrugs were capable of producing high levels of estradiol in the cerebrospinal fluid (CSF), compared to an equivalent intravenous dose. These data suggest that the drug can reach the CSF via a direct pathway through the nasal cavity and as a result may have a significant value in the treatment of Alzheimer's disease [41].

Physical state: particle size and morphology

Particle size and morphology of drug particles constitute important properties for particulate nasal drug products. Particle size and morphology are related to the drug dissolution and should be controlled to obtain suitable drug dissolution properties in the nostrils. In vitro dissolution rates in suitable simulated fluid(s) should be considered. Particle size and morphology are also important to minimize the feel of grittyness and possibly irritation to the nasal cavity. Too fine particles, below five microns may be inhaled into the lungs and should be avoided for nasal products. Generally, particles in the 5-10 micron range are deposited in the nostrils.

Polymorphism

An evaluation and study of the polymorphic forms of drugs administered in particulate form is an important parameter to be considered in nasal drug product development. Polymorphism is known to affect dissolution of drugs and their absorption through biological membranes. The effect of polymorphism on the nasal drug absorption has not been explored to date. However, in view of the information

available on other biological membranes, this factor should be considered.

Formulation properties which affect nasal drug delivery

The specific formulation properties which affect drug absorption depend on the route of administration and the type of dosage form selected.

4. Types of dosage forms and delivery systems

Nasal drops are the simplest and the most convenient nasal pharmaceutical form, but the exact amount of drug delivered is not easily quantified and often result in overdose. Moreover, rapid nasal drainage can occur when using this dosage form. Solution and suspension sprays are preferred over powders sprays because the last one easily prompted the development of nasal mucosa irritation. Recently, gel devices have been developed for a more accurate drug delivery. They reduce postnasal drip and anterior leakage, fixing the drug formulation in nasal mucosa. This enhances the drug residence time and diminishes mucociliary clearance, thereby, potentially increases nasal absorption. Over the last few years, specialized systems such as lipid emulsions, microspheres, liposomes and films have also been developed to improve nasal drug delivery.

Drug concentration, dose and volume of administration

There should be clear positive relationship between absorption and drug concentration upto a certain level. Such a relationship is not always observed. There are many other confounding factors which can influence the nasal membrane transport mechanism and provide a modified absorption profile. 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 dose is increased by increasing formulation volume, there may be a limit as to what extent nasal absorption can be increased. The nostrils can remain 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. A powder form was found to be more effective than liquid formulations because powder is not readily washed out with the nasal secretions.

Viscosity

As formulation viscosity increases, the contact time between drug and nasal mucosa enhances and, thereby, the potential of drug absorption increases. At the same time, high viscosity of formulations interferes with normal ciliary beating and/or mucociliary and, thus, incrases the permeability of drugs. This has been observed during nasal delivery of insulin [42], acyclovir [43] and metoprolol [44]. However, sometimes, enhancing formulation viscosity does not enhance the drug absorption. Generally, a more viscous formulation will provide less efficient systemic nasal drug delivery. Zaki et al. [45] studied the influence of formulation viscosity on the retention time of mwtoclopramide hydrochloride in nasal cavity and on its absorption. They observed that although the residence time enhanced as viscosity increased the drug absorption diminished. This observation has been attributed to a decrease in the drug diffusion from the formulation. On the other hand, it has also been reported that the viscosity of the solution may provide a larger therapeutic period of nasal formulations [45].

Formulation pH

The extent of nasal absorption depends on the pKa of drug and pH at the absorption site, contributing for that also the pH of formulation. It is important to adjust nasal formulations to appropriate pHs for the following reasons:

- To avoid irritation of the nasal mucosa;
- To avoid efficient drug absorption;
- To prevent growth of pathogenic bacteria in the nasal passage;

To avoid nasal irritation, formulation pH should be adjusted between 4.5 and 6.5. The nasal surface pH 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. The physiological properties of drugs should be kept in mind in deciding on formulation pH. Most drugs are absorbed well in their un-ionized form. While it is desirable keep the formulation pH between 4.5 and 6.5, at times a pH lower than 4.5 may have to be chosen to keep an appreciable drug fraction in the un-ionized form.

Formulation osmolarity

In a series of three articles, Ohwaki et al. [46] studied the effects of osmolarity, among other factors, on the nasal absorption of secretin in rats. They found that the absorption was affected by the concentration of sodium chloride in the formulation and the absorption reached a maximum at a 0.462 M sodium chloride concentration. Shrinkage of epithelial cells of the nasal mucosawas observed at this salt concentration. At a formulation pH of about 3, the observed effects may have been a combination effect of the low pH and the salt concentration. Vora et al. [47] have also reported that drug absorption through the nasal mucosa can be substantially affected by formulation tonicity.

Formulation excipients: In nasal formulations, a wide variety of pharmaceutical excipients can be found and they are selected accordingly to their functions. Solubilizers, buffer components, antioxidants, preservatives, humectants, gelling/viscosifying agents, and flavoring or taste masking agents are some of the most usual excipients. Although they are responsible for several nasal irritations, antioxidants, preservatives, humectants and flavoring or taste masking agemts are not expected to alter nasal drug absorption.

Biological factors which affect nasal drug absorption

Nasal blood flow

The nasal mucosa is supplied by rich vasculature and presents a large surface area making it an optimal local for drug absorption. The blood flow rate influences significantly the systemic nasal absorption of drugs, so that as it enhances more drug passes through the membrane, reaching the general circulation. Indeed, bearing in mind that most of drug absorption takes place by diffusion, the blood flow is essential to maintain the concentration gradient from the site of absorption to blood. Hence, it is well known that vasodilation and vasoconstriction may determine the blood flow and, consequently, the rate and extent of drug to be absorbed. The blood vessels in the

nasal mucosa are surrounded by adrenergic nerves which act as alpha adrenoceptors. Stimulation of these receptors has been shown to decrease blood flow and blood content in the nose of animals [48] and humans [49]. The nasal blood is affected by several external and physiological factors such as ambient temperature, humidity, presence of vasoactive drugs, trauma, and inflammation [50] as well as psychological factors such as emotion, fear, anxiety, and frustration [51]. The nasal flow is sensitive to different locally or systemically acting drugs. Drugs such as oxymetazoline [49] and clonidine [52] decrease blood flow whereas histamine [53], albuterol [54], isoproterenol [55], phenylephrine [54] and fenoterol [56] are shown to increase the blood flow. Such effects are important in determining nasal drug absorption due to their effect on blood flow.

Enzymatic activity in the nose

Drugs nasally administered circumvent gastrointestinal and hepatic first-pass effect. However, they may be significantly metabolized in lumen of nasal cavity or during the passage across the nasal epithelial barrier due to the presence of cytochrome P450 dependent monoxygenase, lactate dehydrogenase, oxidoreductase, hydrolases, acid phosphatase and esterase. It has been reported that cytochrome P450 isoenzymes metabolized the drug such as cocaine, nicotine, alcohols, progesterone and decongestants [57]. Similarly, proteolytic enzymes (aminopeptidases and proteases) were found and they are belived to be the major barrier against the absorption of peptide drugs, such as calcitonin, insulin and desmopressin [58]. Thus, enzymes exist in the nasal mucosa may affect the pharmacokinetic and pharmacodynamic profile of nasally applied drugs. In this context, although the nasal first-pass metabolism is usually weaker than hepatic and intestinal ones it cannot be ignored.

Mucociliary clearance

The function of mucociliary clearance system is to remove foreign substances and particles from the nasal cavity, consequently preventing them from reaching the lower airways. Nasally administered formulation can be cleared from the nasal cavity with a half-life of clearance of about 15 min with the result of limiting time available for absorption [59]. The normal mucociliary transit time in humans has been reported to be 12-15 min [60]. Rapid mucocliliary clearance of drug formulations that are deposited in the nasal cavity is thought to be an important factor underlying the low bioavailability of intranasally administered drugs. Some drugs, hormonal changes in the body, pathological conditions, and formulation factors especially rheology are reported to affect mucociliary clearance and in turn exert significant influence on drug permeability.

Physical condition of the nasal mucosa

The condition of the nasal mucosa can have an important effect on drug absorption. There are times when the mucosa is crushing, bleeding, or dry. One may be suffering from rhinorrhea, sinitis, or nasal infection. In people suffering from severe nasal allergies, an excessive nasal secretion can wash away the formulation before the drug has a chance of getting absorbed through the mucosa or before acting locally [61].

Ideal drug candidate for nasal delivery

Based upon an overall review of the literature on the nasal route of drug administration, an ideal nasal drug candidate should possess the following attributes:

Appropriate aqueous solubility to provide the desired dose in a 25-150 µl volume of

- Formulation administered per nostril;
- Appropriate nasal absorption properties;
- No nasal irritation from the drug;
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action;
- Low dose. Generally, below 25 mg per dose;
- No toxic nasal metabolites;
- No offensive odors/aroma associated with the drug;
- Suitable stability characteristics.

Methods used to study nasal absorption in rats

The methods that are used to study nasal absorption are as follows:

In-situ method

Spague-Dawley male rats, weighing ~300 g each, are normally used. The rats are anaesthetized by i.p. injection of 50 mg/kg sodium pentobarbital. After an incision is made in the neck of the rats, the trachea is cannulated with a polyethylene tube. Another tube is inserted through esophagus to the posterior part of the nasal cavity. This tube served to introduce the perfusing solution into the nasal cavity. The nasopalatine is closed with an adhesive agent to prevent the drainage of the drug solution from the nasal cavity into the mouth. Various drug solutions with volume ranging from 3-20 ml are placed in a water jacketed baker (20 ml) and keep at 37°C by means of a circulating water bath. Each solution is circulated through the nasal cavity of the rat by means of a polystaltic pump at a rate of 2-3 ml/min. The perfusion solution passes out from the nostrils through the funnel and into the beaker again. The solution is stirrer constantly using a magnetic stirring bar (Fig. 2). The samples solution is withdrawn by a 100 µl syringe. The extent of absorption is determined over a period of 1 h by analyzing periodically the amount of drug remaining in the perfusing solution. The most significant advantage of this is that one can screen several drugs easily and conveniently using standard analytical procedures. Furthermore, if the study is conducted using different perfusing volume, one can use the easily determined in-situ data to predict the in-vivo rate of absorption.

***In-vivo* in-situ method**

In this method, small volumes of the drug 50-100µl are administered to the nasal cavity. The concentration of the drug in the nasal cavity is determined utilizing simple analytical procedures. Furthermore, the data generated can be used directly to predict in-vivo absorption rates. Thesurgical procedure is similar to that described for the in-situ recirculation studies, except that a glass tube (3 cm long and 0.3 mm in diameter with one end sealed) is inserted into the posterior nasal cavity through the esophagus to keep the solution in the nasal cavity. Prior to administering the drug, the nasal cavity is carefully washed with 10 ml of Ringer's buffer to remove all traces of blood. One hundred-microlitre aliquots of solutions containing

drug are placed in one nostril by means of micropipette. At an appropriate time interval, the nasal cavity is rinsed with 3.9 ml of ringer's buffer using peristaltic pump, and the experiment is terminated. In-vivo method, in this method the drug is directly deposited into the nasal cavity and blood samples are periodically withdrawn and analyzed. In large animals such as dogs, sheep, and monkeys the drug is administered while the animal is under anesthesia and care should be taken to minimize the physical loss of the drug due to drainage. The surgical procedure described by Huang et. al. [62] is performed on an anesthetized rat. Since this method utilizes a closed and confined system, the data obtained is very reproducible and reliable. Furthermore, this model can also be used to predict the absorption profile of the drugs in other species as dogs and humans.

5. Conclusion

Nasal drug delivery is a promising alternative route of drug administration for topical, systemic and central nervous system action. It has advantages in terms of reduces systemic exposure and hence side effects and avoiding first-pass metabolism. However, the intranasal route presents several limitations which must be overcome to develop a successful nasal medicine. Physiological conditions, physicochemical properties of drug and formulation are most important factors that affect nasal absorption. In future, the extensive research is necessary to make this route of delivery more efficient and popular.

6. References

[1] Hicke A.J., Pharmaceutical Inhalation Aerosol Technology, 2nd ed Marcel Dekker, Inc: New York, 2004.

[2] Illum L. Nasal drug delivery-possibilities, problems and solutions. J Control Release.2003; 87: 187–198.

[3] Ugwoke M.I., Verbek N., and Kinget R. J Pharm Pharmacol. 2001; 59: 3–22.

[4] Arora P., Sharma. Gary S. Drug Discov Today. 2002; 7: 967–975.

[5] Marttin E., Nicolaas G.M., Schipper J., Coos V., Frans WH. Adv Drug Del Rev. 1997; 29:13-38.

[6] Choi H.G., Jung J.H., Ryu J.M. Int J of pharm. 1998; 165: 33-44.

[7] CIllum L. Drug Discov Today. 2002; 7:1184-1189.

[8] Graff L.C., Pollock G.M. J Pharm Sci. 2005; 94:1187-1195.

[9] LipworthB.J., and Jackson C.M. Drug Saf. 2000; 23: 11–33.

[10] Wiseman J.W. Gene The. 2001; 8: 1562–1571.

[11] Krishnamoorthy R., and Mitra N.K. Adv Drug Deliv Rev.1998; 29: 135–146.

[12] Duquesnoy C., Mamet J.P., Sumner D., and Fuseau E. Eur J Pharm Sci. 1998; 6:99-104.

[13] Singh kumarArun. Journal of Drug Delivery and Therapeutics. 2012; 23:22-33.

[14] Chajed S., Sangle S and Barhate S,. International journal of pharmaceutical science and research. 2011; 2(6):1322-1336.

[15] Zaheer A., Sachin.,Swamy. Indian Journal of Novel Drug Delivery. Jan-Mar, 2012; 4(1): 2-16.

[16] Behl C,R., Pimplaskar N.K., Sileno A.P., Demeireles J., Romeo VD. Advanced drug delivery Reviews. 1998; 89-116.

[17] Cauna N. Blood and nerve supply of the nasal lining, in: D.F. Proctor, I.B. Andersen (Eds.), Elsevier Biomedical Press, Amsterdam. 1982; 45-69.

[18] Illum, L. Eur J Pharm Sci. 2000; 11:1–18.

[19] Parvathi M. International journal of research in pharmacy and chemistry. 2012; 2(3): 889-895.

[20] Sarkar M.A. Pharm.Res. 1992; 9: 1–9.

[21] Merkus F.W., Verhoef J.C., Schipper N.G., Marttin E. Adv Drug Deliv Rev. 1998; 29:13-38.

[22] Charlton S., Jones N.S., Davis S.S., Illum L. Eur J Pharm Sci. 2007; 30:295-302.

[23] Dondeti P., Zia H., Needham T.E. Int J Pharm. 1996; 127:115-133.

[24] Dahl, R. and Mygind, N. Adv. Drug Deliv. Rev.1998; 29: 3–12.

[25] Machida M. Biol. Pharm. Bull. 1994; 17:1375–1378

[26] Watanabe H., and Tsuru H. Nippon YakurigakuZasshi 1999; 113: 211–218.

[27] Cornaz A.L., and Buri P. Eur. J. Pharm. Biopharm. 1994; 40: 261–270.

[28] Gannu Praveen Kumar and KiranS.. Indian Journal of Pharmaceutical Science & Research. 2012; 2(1):33-41.

[29] Corbo D.C. J. Pharm. Sci. 1990; 79: 202–206.

[30] SakaneT.. Chem. Pharm. Bull. (Tokyo) 1991; 39: 2456–2458.

[31] Ohwaki K., Ando H., Watanabe S., Miyake Y. Chemother.,1992;3:157–164.

[32] Clement P., Roovers M.H., Francillon C., Dodion P. Allergy 1994; 49: 668–672.

[33] Donovan M.D., Flyn G.L., Amidon G.L. Pharm. Res. 1990; 7:863-868.

[34] Ibrahim A., Alsarra A.Y., Hamed., Fars K.A., and Gamal M., Maghraby E., Neuro methods 45, DOI 10.1007/978-1-60761-529- 38.

[35] A.Yamamoto, T. Iseki, M. Ochi-Sugiyama, N. Okada, T. Fujita, S. Muranishi, J Control Release., 2001, 76, 363–74.

[36] M. Hinchcliffe, L. Illum, Adv Drug Deliv Rev., 1999, 35, 199–234.

[37] C. R. Behl, H. K. Pimplaskar, A. P. Sileno, J. Demeireles, V. D. Remo, Adv Drug Deliv Rev., 1998, 29, 89–116.

[38] D. C. Corbo, J. C. Liu, Y. W. Chien, J Pharm Sci., 1990, 79, 202–206.

[39] A.Ninomiya, K. Ogasawara, K. Kajino, A. Takada, H. Kida, Vaccine., 2002, 20, 3123–29.

[40] A.Yang, H. Gao, A. Mitra, J Pharm Sci., 2000, 90, 617–24.

[41] A.M. Al-Ghananeem, A. A. Traboulsi, L. W. Dittert, A. A. Hussain, AAPS Pharm Sci Tech., 2002, 3, 1–8.

[42] A.Heidari, H. Sadrai, J. Varshosaz, Drug Deliv.,2006, 13, 31-8.
[43] I.A. Alsarra, A. Y. Hamed, G. M. Mahrous, G. M. El Maghraby, A. A. Al-Robayan, F. K. Alanazi, Drug DevInd Pharm., 2009, 35, 352-62.
[44] N. Kilian, D. G. Müller, Int J Pharm., 1998, 163, 211-17.
[45] N. M. Zaki, G. A. Awad, N. D. Mortada, S. S. AbdElHady, Int J Pharm., 2006, 327, 89-96.
[46] A.Huang, R. Kimura, R. Nassar, A.A. Hussain, J. Pharm. Sci., 1985, 74, 1298–301.
[47] I.Gonda, E. Gipps, Pharm. Res., 1990, 7, 69–75.
[48] A. Harris, M. Ohlin, E. Svensson, S. Lethagen, I. Nilsson, J. Pharm. Sci., 1989, 78, 470–71.
[49] L. Malm, ActaOtolaryngol. (Stockh.).,1974, 78, 90–7.
[50] H.B. Richerson, P.M. Seeboham, J. Allergy., 1968, 41, 269–84.
[51] M. Bende, Acta. Otol., 1983, 96, 523–27.
[52] P. Olson, M. Bende, Ann. Otol. Rhinol. Laryngol.,1985, 94, 153–57.
[53] A.Paulsson, M. Bende, P. Ohlin, ActaOtolaryngol. (Stockh.).,1985, 99, 140–4.
[54] K. Anderson, M. Bende, Ann. Otol. Rhinol. Laryngol.,1984, 93, 179–82.
[55] M. Bende, K. Flysberg, I. Larsson, P. Ohlin, P. Olson, ActaOtolaryngol. (Stockh.).,1983, 96, 277–80.
[56] M. Lung, J. Wang, Ann. Otol. Rhinol. Laryngol.,1985, 94, 198–201.
[57] S. Dimova, M. E. Brewster, M. Noppe, M. Jorissen, P. Augustijns, Toxicol In Vitro.,2005, 19, 107-22.
[58] V. H. Lee, A. Yamamoto, Adv Drug Deliv Rev., 1990, 4, 171-207.
[59] R. J. Soane, M. Frier, A. C. Perkins, N. S. Jones, S. S. Davis, L. Illum, Int J Pharm., 1999, 178, 55–65.
[60] F.W. Merkus, J. C. Verhoef, N. G. Schipper, E. Marttin, Adv Drug Deliv Rev., 1998, 29, 13–38.
[61] E.L. Smith, R.L. Hill, A. Borman, Biochem. Biophys. Acta., 1958, 29, 207–14.
[62] E.G. Brittebo, J.J. Rafter, Steroid. Biochem. 1984, 20, 1147.