

Review Article

Nasal Drug Delivery: Problem Solution and Its Application

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Received 28 March 2014; received in revised form 12 May 2014; accepted 12 May 2014

Available online 23 June 2014

Abstract

There are various types of drug delivery like parenteral and non parenteral. Nasal drug delivery is one of the alternative and viable route of drug delivery. Nasal route having rich vasculature and highly permeable. Nasal route is more suitable for those drugs cannot be administered orally due to gastric irritation. Nasal route helpful in various disorder. Bearing in mind the intrinsic value of intranasal route to overcome patients compliance concern together with its pharmacokinetic advantages, its appear to be an appropriate route for the treatment of not only for acute but also for chronic nasal diseases. So researcher steps in this field and brings new nasal formulation.

Keywords: Nasal route, Factors, Researchers, Strategy, Application.

1. Introduction

Nasal drug delivery which has been practiced for thousands of years has been given a new lease of life. Nasal therapy, has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called "NASAYA KARMA". Nasal route is permeable to more com-pounds 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. It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins, peptides, harmones and steroids. This indicates the potential value of the nasal route for administration of systemic medications as well as utilizing this route for local effects¹. Nasal area of drug delivery received additional attention with a timely seminar organized by Dr. Y.E. Chien in 1984 the seminar entitled 'Intranasal Drug Administration for Systemic Medications' was instrumental in placing nasally administered medications at the fore front of drug delivery.

There are two books, one written by Chien in 1985 and another by Chien et al. in 1989 provided a comprehensive review of the subject matter and a direction for other researchers to follow². The potential of nasal drug delivery (NDD), including the ability to target drugs across the blood-brain barrier (BBB), is very high and continues to stimulate academic and industrial research groups so that we will keep witnessing increasing number of advanced nasal drug delivery³. The world market has seen an increasing number of systemically acting drugs being marketed as nasal formulations. For example, sumatriptan, zolmitriptan, ergotamine, butorphanol all with the indication for treatment of migraine, where a rapid onset of action is beneficial; estradiol (Servier, <http://www.servier.com>). Where an improved bioavailability as compared to oral delivery has been achieved. A range or number of companies specializing in the development of innovative nasal delivery systems and formulation problems has come to the fore: Nastech, Britannia Pharmaceuticals, Intranasal Technologies, Bentley Pharmaceuticals and West Pharmaceutical Services are actively developing novel nasal formulations for conventional generic drugs (Example-

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Apomorphine, triptans, morphine, midazolam, fentanyl, non-steroid anti-inflammatory drugs), as well as for peptides and proteins (example-leuprolide, parathyroid hormone, insulin, and interferon)⁴

2. Percentage Wise Contribution of Drug Delivery System

Nasal routes contribute only by 2% in drug delivery (see fig.1)⁵

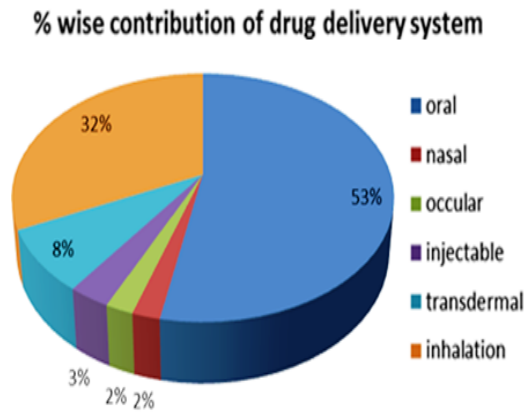


Fig.1: Percentage Wise Contribution of Drug Delivery System.

2.1. Anatomy and physiology of Nose

The human nasal cavity has a total volume of about 16 to 19 ml and total surface area of about 180 cm. It is divided into two nasal cavities via the septum. Some of the regions are described as follows-

2.1.1. The Respiratory region

The respiratory region is the largest having the highest degree of vascularity and is mainly responsible for systemic drug absorption.

2.1.2. The Vestibular region

It is located at the opening of nasal passages and is responsible for filtering out the air borne particles. It is considered to be the least important of the three regions with regards to drug absorption. (See Figure. 2)

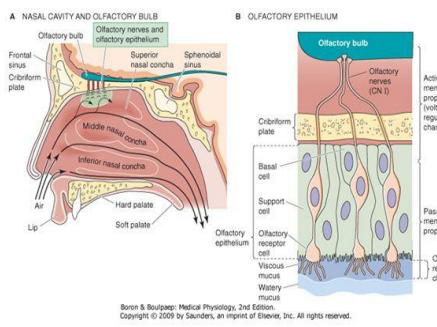


Fig.2: Anatomy and Physiology of Nose.

2.1.3. The olfactory region

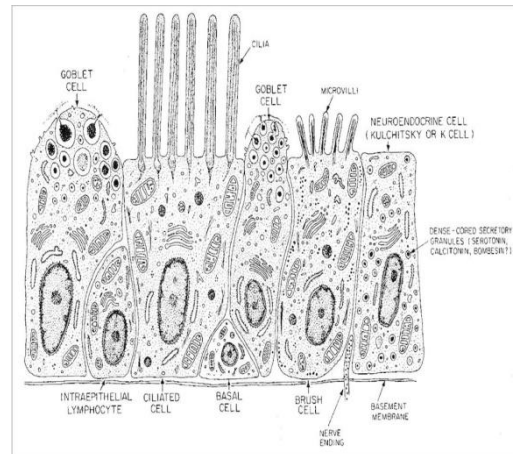


Fig. 3: Cell types of the nasal epithelium showing ciliated cell.

Olfactory region is of about 10 cm² in surface area and it plays a vital role in transportation of drugs to the brain and the cerebrospinal fluid. Human olfactory region comprises of thick connective tissue lamina propria, upon which rests the olfactory epithelium, epithelium consists of three different cells i.e. basal cells, supporting cells and olfactory receptor cells etc. Neurons are interspersed between the supporting cells. The olfactory receptor cells are bipolar neurons with a single dendritic and extending from the cell body to the free apical surface (See Fig.3). Where it ends in an olfactory knob carrying non-motile cilia, which extend above the epithelium. The epithelium of the nasal passage is covered by a mucus layer, which entraps particles. The mucus layer is cleared from the nasal cavity by cilia and is renewed every 10 to 15 minutes the pH of the mucosal secretions ranges from 5.5 to 6.5 in adults. Number of enzyme present in nasal cavity these are Cytochrome P-450, Carboxylesterases and Glutathione S-transferase are present in nasal cavity⁶.

3. Advantages and disadvantages of Nasal Drug Delivery System

Table 1: Advantages and disadvantages of Nasal Drug Delivery System

Advantages	Disadvantages
<ol style="list-style-type: none"> 1. Drug degradation is absent. 2. Hepatic first – pass metabolism is absent. 3. Rapid drug absorption. 4. Quick onset of action. 5. Bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach. 6. Better nasal bioavailability for smaller drug molecules. 7. Convenient route for long term therapy.⁷ 8. Minimal aftertaste 9. Does not require any modification of the therapeutic agent. Example-In neurological and psychiatric disorders. 10. Easy accessibility to blood capillaries⁶ 11. Polar compounds particularly suited for nasal route.⁸ 12. Reduce risk of infectious disease transmission² 13. Does not have any complex formulation requirement⁹. 	<ol style="list-style-type: none"> 1. High permeability of the nasal mucosa.. 2. Lack of adequate aqueous solubility. 3. Entire dose limit volume of 25–200 ml. 4. Less suitable for chronically administered drugs. For example, insulin². 5. Use absorption enhancers. 6. Less absorption surface area is less 7. Once the drug administered cannot be removed. 8. Nasal irritation⁷. 9. Delivery is expected to decrease with increasing molecular weight of drug. 10. Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa. 11. Nasal congestion due to cold or allergies.⁶ 12. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs⁸.

4. MECHANISM OF NASAL ABSORPTION

The absorbed drugs from the nasal cavity must pass through the mucus layer; it is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs are difficult to cross it. The principle protein of the mucus is mucin; it has the tendency to bind to the solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.). So many absorption mechanisms are established earlier but only two mechanisms have been predominantly used, such as:

4.1. First mechanism

It involves an aqueous route of transport, also known as the paracellular route but slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability.

4.2. Second mechanism

It involves transport through a lipoidal route and it is also known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drug also cross cell membranes by an active transport route via

carrier-mediated means or transport through the opening of tight junctions. For examples: chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport⁸.

5. Functional features of nasal cavity and permeability

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. The nasal cavity has a relatively large surface area (approximately ~150–160 cm²) because of the presence of ~400 microvilli per cell and the total volume of nasal secretions is ~15 ml per day under normal physiological conditions.⁹

6. Mechanism of permeation

A drug administered through the nasal cavity can permeate either passively by the paracellular pathway or both passively and actively via the transcellular pathway. Depends on the lipophilicity of the compound. Apart from the passive transport pathways, carrier mediated transport, transcytosis and transport through intercellular tight junctions these are other possible pathways. Lang *et al.* mathematically expressed the effective

permeability coefficient Peff under steady state conditions across excised mucosa.
(See equation 1)-

$$P_{eff} = (dc/dt)_{ss} V / (A CD)$$

Where,

(dc/dt)_{ss} - The time-dependent change of concentration in the steady state,

A - Permeation area,

V-The volume of the receiver compartment and CD- The initial concentration in donor compartment

Fluorophore labelled markers and drugs, in combination with sophisticated microscopy techniques such as confocal laser scanning microscopy have been used in visualizing the permeation pathways. The bioavailability of drug after intranasal administration may be expressed in terms of absolute absorption. In that actual concentration (AC) determined from the area under curve (AUC) following the intravenous (i.v.) and intranasal (I.N.) dose. (See equation 2)

$$AC = \frac{(AUC)_{I.N} (DOSE)_{I.V.}}{(AUC)}$$

Where AUC was extrapolated to an infinite time following administration of single intravenous or intranasal dose.AC can also be calculated from the urinary excretion data following intravenous and intranasal administration of a single dose of drug. It is determined from the total amount of drug excreted in the urine in the metabolized form (AU2). (See equation 3)

$$AC = \frac{(AU2)_{I.N} (DOSE)_{I.V.}}{(AU2)}$$

Equation 3 is valid only when the fraction of drug dose absorbed and excreted in urine is same for both intravenous and intranasal routes. If the body is considered to act as a single compartment, the pharmacokinetics behaviour of drug administered by the Intranasal route may be calculated according to the following model:



Xin - amount of drug administered to the nasal site.

XB - amount of drug in central compartment

V - Apparent volume of distribution

XE -amount of drug eliminated^{9,10}

7. Variable Factors Affecting the Permeability of Drugs through the Nasal Mucosa

7.1. Biological

Although efforts are being made to skillfully modify and explore the structural features and mechanisms of nasal mucosa to increase permeability, this is not advisable because of anticipated alterations in the normal physiology of the nasal cavity, especially during chronic application. These alterations could cause unintended adverse effects and result in pathological implications.

7.1.1. Structural features

Nasal epithelium consist of different types cells so show variation in nasal absorption and because of other factors such as the presence of microvilli, cell density, surface area and the number of cells. The respiratory region is richly supplied with blood, has a large surface area and receives the maximum amount of nasal secretions, rendering it most suitable for the permeation of the compounds.

7.1.2 Biochemical changes

Nasal mucus acts as one of the enzymatic barrier to the delivery of drugs 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, which hampers the absorption of drugs. Some example like the nasal P450-dependent monooxygenase system has been implicated in nasal metabolism of nasal decongestants, alcohols, nicotine and cocaine. Also Enzymes such as peptidases and proteases present in the lumen of the nasal cavity or in the epithelial barrier limit the absorption of drugs, such as calcitonin, insulin, desmopressin and leutinising hormone releasing hormone^{9,11}

7.1.3. Physiological factors

7.1.3.1. Blood supply and neuronal regulation

Nasal mucosa is richly supplied with blood and presents a large surface area making it an optimal location 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. Example Kao et al. stated that nasal absorption of dopamine was relatively slow and incomplete probably due to its own vasoconstrictor effect. Based on these observations, it was concluded that vasoconstriction decrease nasal drug absorption by diminishing the blood flow⁷.

7.1.3.2. Nasal secretions

Production of nasal secretions is done from anterior serous and seromucus glands. Approximately 1.5–2 l ml of mucus is produced daily. The mucus layer probably exists as a double layer (5 mm thick) consisting of periciliary sol phase in which the cilia beat and a superficial blanket of gel is moved forwards by the tip of the cilia. The permeability of drug through the nasal mucosa is affected by viscosity of nasal secretion. It is reported that if the sol layer of mucus is too thin, the viscous surface layer will inhibit the ciliary beating, and if the sol layer is too thick, mucociliary clearance is impaired because contact with cilia is lost. Diurnal variation and circadian rhythms also affect nasal secretions. Impairment or modification of mucociliary clearance affects permeation of the drug by altering the time of contact of drug and mucosa. Solubility of drug in nasal secretions: a drug needs to be solubilized before it permeates. Various studies revealed that the secretion and clearance rates are reduced at night thus altering the permeation of drug. In such cases chronokinetics will dictate the pattern and rate of permeation.

7.1.3.3. Nasal cycle

Nasal cycles of congestion (increased blood supply resulting from parasympathetic stimulation) and relaxation (decreased supply resulting from sympathetic stimulation) regulate the rise and fall in the amounts of drug permeated, respectively⁹.

7.1.3.4 pH of the nasal cavity

It varies between 5.5–6.5 in adults and 5.0–7.0 in infants. A greater drug permeation is usually achieved at a nasal pH that is lower than the drug's pKa because under such conditions the penetrant molecules exist as unionized species. A change in the pH of mucus can affect the ionization and thus increase or decrease the permeation of drug, depending on the nature of the drug. 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 and if possible the formulation should also have buffering capacity⁹.

7.1.3.5. Mucociliary clearance and ciliary beat frequency

The main function of the mucociliary clearance system is to remove foreign substances (bacteria, allergens and so on) and particles from the nasal cavity, thus preventing them from reaching the lower airways. The mucociliary clearance system has been described as a "conveyer belt" in which ciliated cells provide the driving force, and mucus performs as a sticky fluidic belt that collects and disposes of foreign particles. While the effective strokes propel the overlying mucus forward, the underlying periciliary fluid only moves forward and backwards during the beat cycle. Normal mucociliary transit time been reported to be 12 to 15 min. Transit times of more than 30 min are considered to be abnormal, and are indicative of impaired mucociliary clearance. The average rate of nasal clearance is about 8 mm/min, ranging from less than 1 to more than 20 mm/min. Reduced Mucociliary clearance (MCC) and ciliary beating (MCC) increases the time of contact between a drug and the mucus membrane and subsequently enhances drug permeation; whereas, increased MCC decreases drug permeation. Some factors affecting on MCC like drugs, hormonal changes of the body, pathological conditions, environmental conditions and formulation factors (especially rheology are reported to affect the MCC and in turn exert significant influence on drug permeability^{9,12}.

7. 1.4. Pathological conditions

Diseases such as the common cold, rhinitis, atrophic rhinitis and nasal polyposis are usually

associated with mucociliary dysfunctioning, hypo or hypersecretions, and irritation of the nasal mucosa, which can influence drug permeation⁹.

7.1.5. Environmental factors

Temperatures in the range of 24°C cause a moderate reduction in the rate of MCC. A linear increase in ciliary beat frequency occurs with increase in temperature, which in turn influences the properties of the mucous membrane⁹.

7.2. Formulation

7.2.1. Physicochemical properties of drug

7.2.1.1. Molecular weight

One of important factor in nasal drug delivery system. Low molecular weight drugs with are rapidly absorbed through nasal mucosa. The main reasons for this are the high permeability, fairly wide absorption area, porous and thin endothelial basement membrane of the nasal epithelium. Nasal delivery is expected to decrease with increasing molecular weight of the drug. A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Da. Absorption decreases significantly if the molecular weight is greater than 1000 Da except with the use of absorption enhancers. Shape is also important. Linear molecules have lower absorption than cyclic shaped molecules. Literature survey revealed that good bioavailability was observed for drugs with a molecular weight up to 1000 daltons. Fortunately, with the help of permeation enhancers good bioavailability to at least 6000 daltons can be achieved^{13,1}.

7.2.1.2. Size

Particle size and morphology important tool in design of nasal drug delivery. Related to the drug dissolution and should be controlled by suitable drug dissolution properties in the nostrils. In vitro dissolution rates in suitable simulated fluid should be considered. Important to minimize the feel of grittiness 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. The particle size of aerosols is very important with regard to deposition. Particles greater than

10µm are deposited within the upper respiratory tract, those less than 5µm are inhaled, and those less than 0.5µm are exhaled^{14, 15}.

7.2.1.3 Solubility

It not only limits the drug absorption, it can also limit a formulator's ability to formulate a product if the drug is not sufficiently soluble in the desired vehicles. From a mechanistic and thermodynamic standpoint point of view, it is important to learn about the relationship between a drug's saturation solubility and its absorption. The effect of drug solubility on absorption has been extensively explored for gastrointestinal and skin membranes².

7.2.1.4. Dissolution rate

For particulate nasal products, administered as either powder inhalation or in the form of suspensions, the dissolution rate of a drug becomes important. Particles deposited in the nostrils need to be dissolved prior to absorption².

7.2.1.5. Lipophilicity

On increasing in lipophilicity, the permeation of the compound normally increases through nasal mucosa. Although the nasal mucosa was found to have some hydrophilic character, it appears that this mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes. Lipophilic compounds tend to readily cross biological membranes via the transcellular route since they are able to partition into the lipid (bilayer) of the cell membrane and diffuse into and traverse the cell in the cell cytoplasm. Some example like number of lipophilic drugs such as naloxone, buprenorphine, testosterone and 17a-ethinylestradiol, have been shown to be completely or almost completely absorbed nasally in animal models¹⁶.

7.2.1.6. pKa and partition coefficient

According to pH partition theory, unionized species are absorbed better compared with ionized species and the same holds true in the case of nasal absorption. Jiang *et al.* conducted a study to determine the quantitative relationship between the physicochemical properties of drugs and their nasal absorption, using diltiazem hydrochloride and paracetamol as model drugs. The results showed that a quantitative

relationship existed between the partition coefficient and the nasal absorption is constant. 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 mucosa¹⁶.

7.2.1.7. Chemical state

Prodrug is usually referred as promoiety, it is to cover the undesired functional groups with another functional groups. The absorption of peptides like angiotensin II, bradykinin, caulein, carnosine, enkepha-lin, vasopressin and calcitonin are improved by pre-pared into enamine derivatives, these agents showed absorption enhancement with prodrug approach¹.

7.2.1.8. Polymorphism

Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes. It is therefore advisable in case of nasal powders and/or suspensions to study the polymorphic stability and purity of drugs^{17,18}.

7.2.2. Physicochemical properties of formulation

7.2.2.1. pH and mucosal irritancy

The pH of the formulation and nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 because; lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the tissue is susceptible to microbial infection.

Examples -L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments¹. The delivery volume is limited by the size of the nasal cavity. An upper limit of 25 mg/dose and a volume of 0.1-0.2 ml/nostril have been suggested. The pH of a nasal formulation is important for the following reasons,

- To avoid irritation of nasal mucosa
- To prevent growth of pathogenic bacteria in the nasal passage
- To allow the drug to be available in unionized form for absorption

- To maintain functionality of excipients such as preservatives
- To sustain normal physiological ciliary movement¹⁹.

7.2.2.2. Buffer capacity

Nasal formulations are generally administered in small volumes ranging from 25 to 200µL. Hence, nasal secretions may alter the pH of the administrated dose. This can affects the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ²⁰.

7.2.2.3. Solubilisers

Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents are used such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol can be used to enhance the solubility of drugs. cyclodextrins such as HP-β-cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers Other options include the use of surfactants⁶.

7.2.2.4. Preservatives

Nasal formulations usually contain preservatives to protect them from microbial contamination. Some typically used preservatives are parabens, benzalkonium chloride and benzoyl alcohol. Preservatives are used in small quantities and are not likely to affect drug absorption².

7.2.2.5. Antioxidants

Usually, antioxidants do not affect drug absorption or cause nasal irritation. Example- sodium metabisulfite, sodium bisulfate, butylated hydroxytoluene and tocopherol. Chemical or physical interaction of antioxidants and preservatives with drugs, excipients, manufacturing equipment and packaging components should be considered during formulation development¹¹.

7.2.2.6. Humectants

Many allergic and chronic diseases are often connected with crusts and drying of mucous membrane. Therefore humectants can be added especially in gel-based nasal products. Humectants avoid nasal irritation and are not likely to affect drug absorption. Examples like glycerin, sorbitol and mannitol⁶.

7.2.2.7. Drug concentration

Concentration gradient plays very important role in the absorption as well as the permeation process of drug through the nasal membrane due to nasal mucosal damage. Examples for this are nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. Another example is absorption of salicylic acid was found to decline with concentration¹⁹.

7.2.2.8. Osmolarity

Drug absorption can be affected by tonicity of formulation. Shrinkage of 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 a hypertonic solution. Example-Secretin in rats and found that absorption reached a maximum at a sodium chloride concentration of 0.462 M because shrinkage of the nasal epithelial mucosa was observed at this salt concentration This results in to increased permeation of the compound resulting from structural changes and was further confirmed when sorbitol was used as an osmoregulatory agent. The authors found that permeation of secretin subsequently decreased and therefore, isotonic solutions are usually preferred for administration^{11,14}.

7.2.2.9. Viscosity

A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs⁸

7.2.2.10. Drug distribution

The absorption and bioavailability of the nasal dosage forms mainly depends on the site of disposition. The mode of drug administration could affect the distribution of drug in nasal cavity, which in turn will determine the absorption efficiency of a drug. The anterior portion of the nose provides a prolonged nasal residential time for disposition of formulation, it enhances the absorption of the drug. And the posterior chamber of nasal cavity will use for the deposition of dosage form; it is eliminated by the mucociliary clearance process and hence shows low bioavailability¹.

7.2.2.11. Area of nasal membrane exposed

One of the study conducted using 40 mg progesterone ointment, absorption was compared between applications to one nostril with application to both nostrils. Increased bioavailability was observed when ointment was applied in both the nostrils concluding that as the area of mucus membrane exposed increases, it should result in increased permeation⁹.

7.2.2.12. Volume of solution applied

The volume that can be delivered to the nasal cavity is restricted to 0.05–0.15 ml. Different approaches have been explored to use this volume effectively including the use of solubilizers, gelling, or viscofying agents. The use of solubilizer increases the aqueous solubility of insoluble compounds and gelling agents decrease the drainage and result in an increase in the retention time of the drug in contact with mucus membranes.

7.2.2.13. Dosage form

Nasal drops are the simplest and most convenient dosage form but the exact amount that can be delivered cannot be easily quantified and often results in overdose. Moreover, rapid nasal drainage is a problem with drops. Solution and suspension sprays are preferred over powder sprays because powder results in mucosal irritation. Recently, metered-dose gel devices have been developed that accurately deliver drug. Gels reduce the postnasal drip and anterior leakage, and localize the formulation in mucosa. Specialized systems such as lipid emulsions microspheres and lactose, liposomes, proliposomes, films and niosomes have been developed for nasal delivery. These offer a better chance of permeation for the drugs as they provide an intimate and prolonged contact between the drug and the mucosal membrane.

7.3. Device related

7.3.1. Particle size of the droplet or powder

The particle size of the droplet produced depends on the shape and size of the device used. If the particle size produced is <10 µm, then particles will be deposited in the upper respiratory tract, whereas if particle size is <0.5 µm then it will be exhaled. Therefore particles or droplets with size between 5–7 µm

will be retained in the nasal cavity and subsequently permeated⁹.

7.3.2. Site and pattern of disposition

The site of disposition and distribution of the dosage forms are mainly depends on delivery device, mode of administration, physicochemical properties of drug molecule¹.

8. Types of dosage form

8.1 Nasal drop

Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays¹⁷.

8.2. Nasal sprays

Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose anywhere from 25 to 200 µL. Solution and suspension sprays are more preferred over powder sprays because powder results in mucosal irritation²⁰.

8.3. Nasal powders

In solution and suspension dosage forms stability problem occur so cannot be developed. The advantages to the nasal powder dosage forms are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and excipients²⁰.

8.4. Gels

Thickened solutions or suspensions, of high-viscosity are called as a nasal gels. The advantages of a nasal gel include the reduction of post-nasal dripping due to its high viscosity, reduction of the taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients, and target delivery to the mucosa for better absorption. Example like vitamin B12 nifedipine, rizatriptan and apomorphine. Chitin and chitosan have been also suggested for use as vehicles for the sustained release of

drugs. Example-indomethacin and papaverine hydrochloride^{20, 21, 22}.

8.5 Nasal insert

Nasal inserts are novel, bioadhesive, solid dosage forms for prolonged systemic drug delivery via the nasal route. The principle of the dosage form is to imbibe nasal fluid from the mucosa after administration and to form a gel in the nasal cavity to avoid foreign body sensation⁵.

8.6. Microspheres

Microspheres prepared by using different types of materials and have been evaluated in vivo as nasal drug delivery systems. Degradable starch microspheres increase the absorption of insulin, gentamicin, human growth hormone, metoclopramide and desmopressin. Dextran microspheres have been used in vivo as a delivery system for insulin and octreotide have also been evaluated in vitro as a potential delivery system for nasally administered nicotine. Hyaluronic acid ester microspheres increase the absorption of insulin and albumin microspheres have been used to deliver propranolol. Polyacrylic acid microspheres and polyvinyl alcohol microspheres have as yet only been evaluated in vitro as potential nasal drug delivery systems²³.

8.7. Vesicular system

Alternative terminologies have been used to describe such vesicular systems. These included liposome, noisome, transfersomes, ethosomes, vesosomes, colloidosomes, and pharmacosomes. Encouraging results possibility of achieving many objectives such as systemic delivery of small and large molecular weight drugs.

Table 2: Vesicular system and drugs^{24,25,26}

Sr. No	Vesicular System	Drugs incorporated
1	Liposomes	Diphenhydramine, HIVgp160-encapsulated hemagglutinating virus, rivastigmine and M. tuberculosis vaccines (DNA-hsp65).
2	Proliposomes	Nicotine
3	Proniosomes	Flurbiprofen, Frusemide, Estradiol and Losartan potassium

8.8. Nanoparticles

Gao X. et. al studied nanoparticles with lectins opened a novel pathway to improve the brain uptake of agents loaded by biodegradable Polyethylene Glycol and Poly Lactic Acid nanoparticles following intranasal administration. Other example losartan potassium^{11,27}.

8.9. Microemulsion and nanoemulsion

Intranasal microemulsion is one of the focused delivery options for noninvasive drug delivery to systemic circulation. Zhang et al (2004) studied the brain uptake of nimodipine by intranasal administration of nonionic surfactant based microemulsion and found three fold higher of nimodipine and higher ratios of AUC in brain tissues and cerebrospinal fluid to that in plasma. Vyas (2006) has reported that microemulsion formulations of clonazepam incorporated with mucoadhesive agents exhibited faster onset of action followed by prolonged duration of action in the treatment of status epilepticus. Mukesh *et al* (2008) studied the intranasal delivery of risperidone and concluded that significant quantity of risperidone was quickly and effectively delivered to the brain by intranasal administration of mucoadhesive nanoemulsion of risperidone¹⁵.

8.10. Nasal suspension and emulsion

Nanoemulsions increase absorption by solubilizing the drug in the inner phase of an emulsion and prolonging contact time between emulsion droplets and nasal mucosa. Example- A lipid soluble rennin-inhibitor was incorporated into oil in water emulsion. Enhanced and prolonged *in vivo* nasal absorption was observed in emulsion compared to aqueous suspension. Other drugs which have been formulated for nasal delivery are insulin and testosterone²⁸.

8.11. Organogels

Organogel are semisolid system in which an organic liquid phase is immobilized by a three-dimensional network composed of self-assembled, intertwined gelator fibres. The 3-dimensional network of Sorbitone Mono Sterate molecules controls the diffusion of drug release. The organogel system on nasal mucosa during diffusion is dynamic in nature and changes continuously with the time of diffusion. The water penetration in the

organogel network results in percolation and emulsification of organogel, thus affecting the release. The surface epithelium lining and the granular cellular structure of treated nasal mucosa were intact. The effect of tween surfactants on gel strength and *in vitro* nasal diffusion was reported. Organogels provided an effective barrier for diffusion. Example- propranolol^{29,30}.

8.12. Nasal vaccines

Nasal mucosa is the first site of contact with inhaled antigens and therefore, its use for vaccination, systemic as well as local immune response done especially against respiratory infections alternative to parental route. Because it is able to 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 03 viruses¹⁸.

9. Strategies

9.1. Prodrug

The term 'prodrug' was coined by Albert in 1951 and it is used to describe compounds that undergo biotransformation prior to exhibiting their pharmacological effect. Prodrugs have been used to overcome drugs' bad taste, poor solubility, insufficient stability, incomplete absorption across biological barriers and premature metabolism to inactive or toxic species. Once the drug in blood stream, the prodrug must be quickly converted to the parent drug. For example like, L-Dopa is poorly soluble in water, so it is very difficult to develop a corresponding intranasal aqueous formulation with an effective dose. Kao et al. produced various prodrugs of L-Dopa and observed that their solubility enhanced significantly in comparison with the parent drug allowing, hence, the development of adequate nasal formulations. Furthermore, their nasal administration resulted in a rapid and complete absorption to the systemic circulation, where quick conversion to L-Dopa takes place. An alternative approach to the use of prodrugs in order to increase drug solubility is the use of co-solvents³¹.

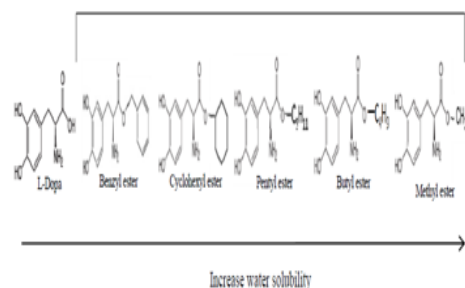


Fig. 4: L-Dopa prodrugs.

9.2. Enzyme inhibitors

Nasal metabolism of drugs can be eliminated by using the enzyme inhibitors. Example proteins and peptide, enzyme inhibitors like peptidases and proteases are used. The other enzyme inhibitors commonly use like tripsin, aprotinin, borovaline, amas-tatin, bestatin and boroleucin inhibitors¹.

9.3. Absorption enhancers

The formulation may require nasal absorption enhancers when the drug is a polar or a macromolecule. The main limiting factor associated with the addition of enhancers to a nasal formulation is the potential toxicity of the nasal mucosa. Nasal absorption enhancers should be non-irritating, non-toxic and non-allergic or at least to have immediate reversible effects. Moreover, they should be systemically inert in the concentrations used. A large number of absorption enhancers used in combination with drugs increase the permeation of compounds by,

1. Increasing fluidity of the membrane,
2. Decreasing viscosity of the mucosal layer,
3. Inhibiting the proteolytic enzymes,
4. Distributing the tight junctions,
5. Increasing paracellular or transcellular transportation, increasing blood flow, and
6. Dissociating protein aggregation or initiating pore formulation, or by a combination of these factors. Apart from this, mucoadhesive dosage forms have also been shown to increase the permeation of compounds¹¹.

9.4. Permeation enhancers

Small and large hydrophilic drugs may be poorly permeable across nasal epithelium and may show an insufficient bioavailability. Their permeation can improve by administered in combination with absorption enhancers which

induce reversible modifications on the structure of epithelial barrier. Some mucosal penetration enhancers and their mechanism of action⁶.

Table 3: Permeation Enhancer.

Classification	Examples	Mechanism
Surfactants	Anionic: Sodium lauryl sulphate	Perturbation of intercellular lipids, Protein domain integrity, Distrusts membrane,
	Cationic: Cetylpyridinium Chloride Nonionic: Poloxamer, Span, Tween	
Bile salts	Sodium glycodeoxycholate, Sodium glycocholate, Sodium taurodeoxycholate,	Distrusts membrane, Open tight junctions, Mucolytic activity
	α, β, γ Cyclodextrin, Methylated β-Cyclodextrins	Inclusion of membrane Compounds, Open Tight junctions Increase fluidity of phospholipid domains, Distrusts membrane
Fatty acids	Oleic acid, Lauric acid, Caprylic acid, Phosphotidylcholine	Ionic interaction with negative charge on the mucosal surface
Cationic compounds	Poly-L-arginine, L-lysine	
Bioadhesive Materials	Carbopol, Starch, Chitosan	Reduce nasal clearance, Open tight junctions

9.5. Structural modification

Modification of drug structure without altering pharmacological activity is one of the lucrative ways to improve the nasal absorption. Commonly used to modify the physicochemical properties of a drug such as molecular size, molecular weight, PKa and solubility are favorable to improve the nasal absorption of drug. Example-Chemical

modification of salmon calcitonin to ecatonin (C-N bond replaces the S-S bond) showed better bioavailability than salmon calcitonin⁸.

9.6. CO solvent

An alternative approach to the use of prodrugs. Co-solvents mostly used in intranasal formulations include glycerol, ethanol, propylene glycol, and polyethylene glycol. Since they should be,

1. Nontoxic,
2. Pharmaceutically acceptable, and
3. Nonirritant to nasal mucosa³¹

9.7. Residence time

Mucociliary clearance acts to remove the foreign bodies and substances from nasal mucosa as quickly as possible. One way of delaying clearance is to apply the drug to the anterior part of the nasal cavity, an effect that is largely determined by the type of dosage form used. The preparation could also be formulated with polymers such as methylcellulose, hydroxypropylmethyl cellulose or polyacrylic acid, in which incorporation of polymer increases viscosity of the formulation and also acts as a bio adhesive with mucus. Other technique like biodegradable starch microsphere.³²

9.8. Mucoadhesive drug delivery

Parenteral drug administration has a lot of advantages compared to the other routes of drug administration. In case of non-parenteral routes the bioavailability is usually much less than 100%.The list of nasal drug products in the market or at various stages of preclinical and clinical development is ever increasing these developments are supported by the recognition of the advantages the nose presents for drug delivery purposes. These include:

1. A large surface area nasal epithelium.
2. 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.
3. A porous endothelial basement membrane that poses no restriction to transporting the drug into general circulation.
4. Avoiding the first pass metabolic effect.

5. In some cases, drugs can be absorbed directly into the central nervous system (CNS) after nasal administration by passing the tight blood–brain barrier.

6. Generally speaking, 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.

7. Realization of pulsatile delivery of some drugs like human growth hormone, insulin, etc.

8. The nose is amenable to self-medication .The risk of over-dosage is low and nasal clavage can be used to remove unabsorbed excess drug.

9. Reformulation of existing drugs as NDD products offers companies the possibility to extend the life cycle of their products³.

9.9. Particulate drug delivery

Particle design is an increasingly important role in absorption enhancement. Microspheres, nanoparticles and liposome are all systems which can be used as carriers to encapsulate an active drug. The properties of these can be varied to maximize therapeutic efficacy. Overall, this can result in increased absorption efficacy and stability and reduced toxicity of the active ingredient. Example- Liposome is amphiphilic in nature are well characterized for favorable permeation of drugs through the biological membranes, so the water soluble drugs have been delivered to nasal drugs. Cationic liposomes are having good permeation capacity than negatively charged anionic liposome¹.

10. Application

10.1. Epilepsy and schizophrenia

Kwatarikar *et al.* prepared micro emulsion containing valproic acid showed a rational diffusion efficiency and better brain bioavailability efficiency. Lorazepam is a poorly water-soluble drug which can be used as tranquillizer, muscle relaxant, sleep inducer, sedative and antiepileptic agent. Co-solvent based parenteral formulations however, have several disadvantages, such as pain and tissue damage at the site of injection and precipitation of the drug on dilution in several cases. So Amit *et al.* Prepared lorazepam microemulsions and demonstrated that microemulsion have very low hemolytic potential and exhibit good physical and

chemical stability and can be considered as a viable alternative to the currently marketed lorazepam formulations

10.2. Migraine

Migraine treatment has evolved in the scientific arena, and opinions differ on whether migraine is primarily a vascular or a neurological dysfunction. Sumatriptan is rapidly but incompletely absorbed following oral administration and undergoes first-pass metabolism, resulting in a low absolute bioavailability of 14% in humans. The transport of Sumatriptan across the blood-brain barrier (BBB) is very poor. Studies have demonstrated that intranasal administration offers good result.

10.3. Antidepressant

Tiwari *et al.* developed eucalyptus oil microemulsion for intranasal delivery to the brain Demonstrated that the microemulsion of eucalyptus oil is cost effective and an efficient formulation which provides the rapid onset in soothing stimulant and antidepressant action.

10.4. Angina pectoris and deflect neurological diseases

Qizhi Zhang prepared microemulsion to improve the solubility and enhance the brain uptake of nimodipine (NM), which was suitable for intranasal delivery. The uptake of NM in the olfactory bulb from the nasal route was three folds, compared with intravenous (i.v.) injection. The ratios of AUC in brain tissues and cerebrospinal fluid to that in plasma obtained after nasal administration were significantly higher than those after i.v. administration. So promising approach for intranasal delivery of NM for the treatment and prevention of neurodegenerative diseases³³.

10.5. Non Peptides and peptides

Drugs with extensive pre-systemic metabolism, some of nonpeptide drugs being studied for nasal delivery and have shown good bioavailability by this route includes. Also peptides and proteins like insulin, calcitonin, pituitary hormones also given through nasal route¹⁰.

Table 4: Non Peptides and peptides

Sr. No	Non peptides
1	Adrenal corticosteroids
2	Sex hormones: 17 β -estradiol, progesterone, norethindrone, and testosterone.
3	Vitamins: vitamin B12
4	Cardiovascular drugs : hydralazine, Angiotensin II antagonist, nitroglycerine, isosobide dinitrate, propranolol, and colifilium tosylate.
5	Autonomic nervous system a. Sympathomimetics: Ephedrine, epinephrine, phenylephrine, b. Xylometazoline, dopamine and dobutamine. c. Parasympathomimetics: nicotine, metacholine d. Parasympatholytics: scopolamine, atropine, ipatropium
6.	Central nervous systems stimulants: cocaine, lidocaine
7	Narcotics and antagonists: bupemorphine, naloxane
8	Histamine and antihistamines: disodium cromoglycate, meclizine
10	Antimigrane drugs: diergotamine, ergotamine, tartarate
11	Phenicillin, cephalosporins, gentamycin
12	Antivirals : Phenyl-p-guanidine benzoate, enviroxime.
13	Inorganic compounds: Inorganis salts, colloidal gold, colloidal carbon,

10.6. Analgesics

Pain management and nasal drug delivery clearly combine to meet the needs of a growing and underserved marketplace. The convergence of pain management and nasal drug delivery may prove to be very fortuitous to those who are suffering with acute, moderate-to severe and breakthrough pain. Nasal delivery of analgesics will offer a non-invasive, fast-acting, efficacious means to relieve that pain. Example-Morphine³³.

10.7. In cancer

In cancer pain management nasal route play an important role. For example-Newer opioids Cancer pain management necessitates the use of opioids when pain is moderate or

severe. Opioids need to be versatile and effective³⁴.

10.8. Delivery of diagnostic

- Phenol sulfonaphthalein- kidney function
- Secretin- pancreatic disorders
- Pentagastrin-secretory function of gastric acid³³

Conclusion

Helpful in development and design of dosage form like safe, efficacious formulation for simple painless and long term therapy. To the best of our knowledge, no studies reported in literature addressed the relative contribution of mucoadhesion, tight junction opening and enzyme inhibition to the overall nasal absorption enhancement of a drug molecule.

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Source of Support: Nil. Conflict of Interest: None declared
