



ISSN: 2231-3354
Received on: 27-08-2011
Revised on: 03-09-2011
Accepted on: 07-09-2011

Advances in nasal trans-mucosal drug delivery

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ABSTRACT

Transmucosal nasal delivery is a promising drug delivery option where common drug administrations, such as intravenous, intramuscular, or oral are inapplicable. Recently, it has been shown that many drugs have better bioavailability by nasal route than the oral route. This has been attributed to rich vasculature and a highly permeable structure of the nasal mucosa coupled with avoidance of hepatic first-pass elimination, gut wall metabolism and/or destruction in the gastrointestinal tract. The physiology of the nose presents obstacles, but offers a promising route for non-invasive systemic delivery of numerous therapies and debatably drug delivery route to the brain. Intranasal microemulsions, gels and microspheres have gained increased interest in recent years as a delivery system for protein and peptides through the nasal route. Thus this review focuses on nasal drug delivery, various aspects of nasal anatomy and physiology, nasal drug absorption mechanisms, various nasal drug delivery systems, and their applications in drug delivery.

Key words: Nasal, Gel, Transmucosal, Delivery, *in-situ*.

INTRODUCTION

Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents (Krishnamoorthy and Ashim, 1998). In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal therapy, has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called "NASAYA KARMA" (Chein, 1989). Nasal drug delivery which has been practiced for thousands of years has been given a new lease of life. It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides. One of the reasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the mucociliary clearance mechanism (Rathananand et al, 2007). The nasal route circumvents hepatic first pass elimination associated with the oral delivery: it is easily accessible and suitable for self-medication. During the past several decades, the feasibility of drug delivery via the nasal route has received increasing attention from pharmaceutical scientists and clinicians. Drug candidates ranging from small metal ions to large macromolecular proteins have been tested in various animal models. It has been documented that nasal administration of certain-hormones and steroids have resulted in a more complete absorption. This indicates the potential value of the nasal route for administration of systemic medications as well as utilizing this route

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for local effects (Hussain et al, 1990). For many years drugs have been administered nasally for both topical and systemic action. Topical administration includes the treatment of congestion, rhinitis, sinusitis and related allergic or chronic conditions, and has resulted in a variety of different medications including corticoids, antihistamines, anti-cholinergic and vasoconstrictors. In recent years, increasing investigations of the nasal route have focused especially on nasal application for systemic drug delivery (Kublik et al, 1998). Only a few nasal delivery systems used in experimental studies are currently on the market to deliver therapeutics into the nasal cavities, i.e. nasal drops as multiple or single-dose formulation, aqueous nasal sprays, a nasal gel pump, pressurized MDIs and dry powder inhalers. Intranasal delivery is currently being employed in treatments for migraine, smoking cessation, acute pain relief, osteoporosis, nocturnal enuresis and vitamin-B12 deficiency. Other examples of therapeutic areas under development or with potential for nasal delivery include cancer therapy, epilepsy, antiemetics, rheumatoid arthritis and insulin-dependent diabetes.

NASAL ANATOMY AND PHYSIOLOGY OF THE NOSE

The human nasal cavity has a total volume of about 16 to 19 ml, and a total surface area of about 180 cm², and is divided into two nasal cavities by the septum. The volume of each cavity is approximately 7.5 ml, having a surface area approximately 75 cm². Post drug administration into the nasal cavity, a solute can be deposited at one or more of anatomically distinct regions, the vestibular, respiratory and olfactory regions showing in figure-1 (Pires et al, 2009).

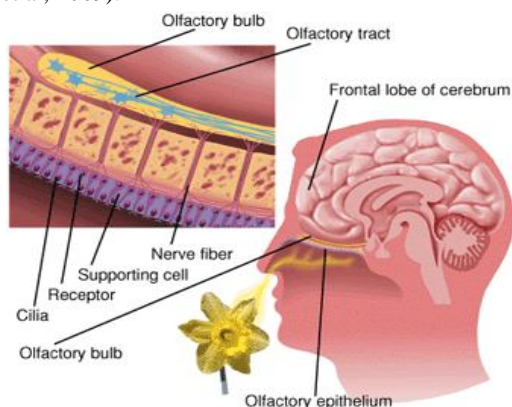


Fig 1: Nasal mucosa

REASON FOR DEVELOPMENT OF NASAL DELIVERY

Nasal drug delivery is a useful delivery method for drugs that are active in low doses and show minimal or no oral bioavailability. The nasal route circumvents hepatic first pass elimination associated with the oral delivery; it is easily accessible and suitable for self-medication. Currently, two classes of nasally delivered therapeutic agents are on the market. The first one comprises low molecular weight and hydrophobic drugs for the treatment of the nasal mucosa and sinus, including decongestants, topical steroids, antibiotics and other (OTC) products. The second class encompasses a few drugs, which have sufficient nasal

absorption for displaying systemic effects. Important candidates are the compounds, generally administered by injection and hardly absorbed after oral administration, due to their instability in the gastrointestinal tract, poor absorption properties, and their rapid and extensive biotransformation (Druce, 1986).

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.) (Illum et al, 1999). So many absorption mechanisms were established earlier but only two mechanisms have been predominantly used, such as-

(a) First mechanism- It involves an aqueous route of transport, which is 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 (Aurora, 2002).

(b) 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 which is showing in figure-2 (Dodane et al, 1999).

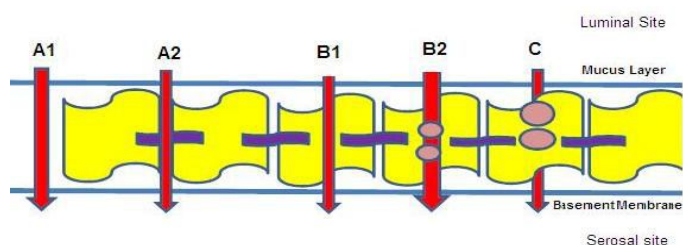


Fig 2 (A1) Intercellular spaces, (A2) Tight junctions, (B1) Passive diffusion, (B2) Active transport, (C) Transcytosis

For examples: chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport (Remo et al 1998).

BARRIERS TO NASAL ABSORPTION

Nasal drug delivery system is considered has a profitable route for the formulation scientist because it has easy and simple formulation strategies. Intra-nasally administered drug products therapeutic efficacy and toxicities are influenced by number of factors (Striebel et al, 1993). Following factors are the barriers to the absorption of drugs through nasal cavity.

i) Low bioavailability- Lipophilic drugs are generally well absorbed from the nasal cavity compared to polar drugs. The

pharmacokinetic profiles of lipophilic drugs are often identical to those obtained after an intravenous injection and bioavailability approaching 100%. A good examples of this is the nasal administration of Fentanyl where the T_{max} for both intravenous and nasal administration have been shown to be very rapid (7 min or less) and the bioavailability for nasal anterior part of the nasal cavity can decrease clear administration was near 80%. The most important factor limiting the nasal absorption of polar drugs and especially large molecular weight polar drugs such as peptides and proteins is the low membrane permeability. Drugs can cross the epithelial cell membrane either by the transcellular route exploiting simple concentration gradients, by receptor mediated or vesicular transport mechanisms, or by the paracellular route through the tight junctions between the cells. Polar drugs with molecular weights below 1000 Da will generally pass the membrane using the latter route (McMartin et al, 1987). Larger peptides and proteins have been shown to be able to pass the nasal membrane using an endocytotic transport process but only in low amounts (Inagaki et al, 1985).

ii) Low membrane transport -Another importance factor is low membrane transport is the general rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism. This is especially the case for drugs that are not easily absorbed across the nasal membrane. It has been shown that for both liquid and powder formulations, that are not mucoadhesive, the half life of clearance is in the order of 15–20 min (Soane et al 1999). It has further been suggested that the deposition of a formulation in the anterior part of the nasal cavity can decrease clearance and promote absorption as compared to deposition further back in the nasal cavity (Harris et al, 1986).

iii) Enzymatic Degradation- Another contributing (but normally considered less important) factor to the low transport of especially peptides and proteins across the nasal membrane is the possibility of an enzymatic de-gradation of the molecule either within the lumen of the nasal cavity or during passage across the epithelial barrier. These sites both contain exo-peptidases such as mono- and di-aminopeptidases that can cleave pep-tides at their N and C termini and endopeptidases such as serine and cysteine, which can attack internal pep-tide bonds (Lee, 1988). The use of enzyme inhibitors and/or saturation of enzymes may be approaches to overcome this barrier (Morimoto, 1995).

FACTORS AFFECTING THE CHARACTERISTICS OF NASAL DRUG DELIVERY:

1-PHYSICOCHEMICAL PROPERTIES OF DRUGS

i. Chemical form

The chemical form of a drug is important in determining absorption. For example, conversion of the drug into a salt or ester form can also alter its absorption. Huang et al (1985) studied the effect of structural modification of drug on absorption. It was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of L-Tyrosine.

ii. Polymorphism

Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes.

iii. Molecular weight

A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Dalton. Absorption decreases significantly if the molecular weight is greater than 1000 Dalton except with the use of absorption enhancers. Shape is also important. Linear molecules have lower absorption than cyclic shaped molecules.

iv. Particle size

It has been reported that particle sizes greater than 10µm are deposited in the nasal cavity.

v. Solubility & dissolution rate

Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared away, no absorption occurs.

FORMULATION FACTORS

i. pH of the formulation

Both the pH of the nasal cavity and pKa of a particular drug need to be considered to optimize systemic absorption. Nasal irritation is minimized when products are delivered with pH, in the range of 4.5 to 6.5. Also, volume and concentration are important to consider. The delivery volume is limited by the size of the nasal cavity. An upper limit of 25 mg/dose and a volume of 25 to 200 µL/ nostril have been suggested:

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

Lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the nasal tissue is susceptible to microbial infection. It is therefore advisable to keep the formulation at a pH of 4.5 to 6.5, keeping in mind the physicochemical properties of the drug as drugs are absorbed in the unionized form.

ii. Buffer capacity

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

iii. 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.

iv. Gelling / Viscosity building agents or gel-forming carriers

Pennington et al (1988) demonstrated that increase in solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations. Suzuki et al (1999) showed that a drug carrier such as hydroxypropyl cellulose was effective in improving the absorption of low molecular weight drugs but did not produce the same effect for high molecular weight peptides.

v. Solubilizers

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

vi. Preservatives

Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations. Van De Donk et al (1980) showed that mercury containing preservatives have a fast and irreversible effect on ciliary movement and should not be used in nasal systems.

vii. Antioxidants

Usually, antioxidants do not affect drug absorption or cause nasal irritation. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylated hydroxyl toluene and tocopherol.

viii. 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. Common examples include glycerin, sorbitol and mannitol.

ix. Drug concentration, dose & dose volume

Drug concentration, dose and volume of administration are three interrelated parameters that impact the performance of the nasal delivery performance. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments.

x. Role of absorption enhancers

Absorption enhancers may be required when a drug

exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation by amino peptidases. Osmolarity and pH may accelerate the enhancing effect. Absorption enhancers improve absorption through many different mechanisms, such as increasing membrane fluidity, increasing nasal blood flow, decreasing mucus viscosity, and enzyme inhibition.

PHYSIOLOGICAL FACTORS

i. Effect of deposition on absorption

Deposition of the formulation in the anterior portion of the nose provides a longer nasal residence time. The anterior portion of the nose is an area of low permeability, while posterior portion of the nose is where the drug permeability is generally higher, and provides shorter residence time.

ii. Nasal blood flow

Nasal mucosal membrane is very rich in vasculature and plays a vital role in the thermal regulation and humidification of the inhaled air. The blood flow and therefore the drug absorption will depend upon the vasoconstriction and vasodilatation of the blood vessels.

iii. Effect of enzymatic activity

Several enzymes that are present in the nasal mucosa might affect the stability of drugs. For example, proteins and peptides are subjected to degradation by proteases and amino-peptidase at the mucosal membrane. The level of amino-peptidase present is much lower than that in the gastrointestinal tract. Peptides may also form complexes with immunoglobulin (Igs) in the nasal cavity leading to an increase in the molecular weight and a reduction of permeability.

iv. Effect of mucociliary clearance

The absorption of drugs is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered showing in figure- 3.

v. Effect of pathological condition

Intranasal pathologies may affect the nasal mucociliary transport process and/or capacity for nasal absorption.

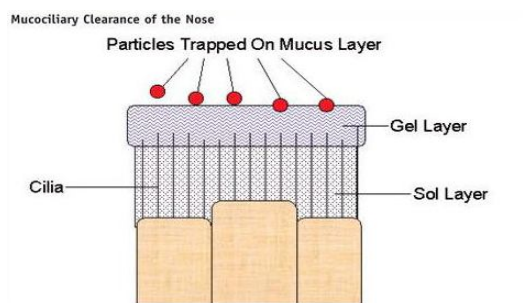
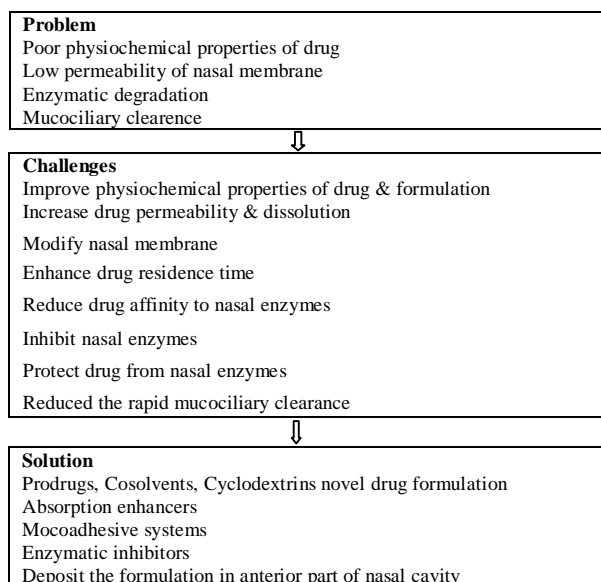


Fig 3 Effect of mucociliary clearance on nasal drug absorption.

CHALLENGES AND OPPORTUNITIES FOR NASAL DELIVERY SYSTEMS

Existing nasal delivery devices such as spray pumps and pipettes cannot fully exploit the described potential advantages of nasal delivery. A large fraction of the dose is deposited on the anterior segment lined by skin, which is not the target for either topical drugs or systemic drugs. Drugs transported along the floor of the nose may cause bad taste and irritation and reduce patient acceptance. Finally, inadequate and variable deposition in the remote region housing the openings to the sinuses and middle ears, as well as the olfactory region, represents a real challenge for extended use of nasal administration of drugs and vaccines. This applies in particular to the new advanced and expensive drugs requiring demanding combination of reliable dosing, high patient compliance and reproducible bio-availability to ensure their efficacy and safety. Regarding actual formulation, most nasal products are currently formulated as liquids and delivered by metered spray pumps.



CURRENT APPROACHES FOR NASAL PERMEATION ENHANCEMENT

Bioavailability of nasally administered drugs is particularly restricted by low drug solubility, rapid enzymatic degradation in nasal cavity, poor membrane penetration and rapid MCC. Thus several approaches have been suggested to overcome these limitations.

1. Prodrugs

Intranasal drugs are commonly administered as solutions or as powder formulations which need to undergo a dissolution process before absorption. Lipophilic drugs easily pass through biomembranes, however they are poorly water soluble. In this way, they should be administered as a prodrug with higher hydrophilic character in order to make possible the production of an aqueous nasal formulation with a suitable concentration. Once in the blood

stream, the prodrug must be quickly converted to the parent drug. 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 (Kao et al, 2000).

Similar results were obtained for testosterone which is also poorly water-soluble (Wang et al, 2005). In contrast, very hydrophilic polar drugs may not have the ability to cross biomembranes. Therefore, if they are administered as prodrugs with higher lipophilic character, the penetration through the membrane may increase. Some researchers have also used the prodrug approach for improving enzymatic stability of drugs. For example, Yang et al stated that L-aspartate- β -ester prodrug of acyclovir was more permeable and less labile to enzymatic hydrolysis than its parent drug (Yang et al, 2001). In addition, the potential use of prodrugs to protect peptide drugs from nasal enzymatic degradation has been discussed and suggested as a powerful strategy to increase the bioavailability of peptides when administered intranasally (Costantino et al, 2007).

2. Co-Solvents

An alternative approach to the use of prodrugs in order to increase drug solubility is the use of co-solvents. Co-solvents most used in intranasal formulations include glycerol, ethanol, propyleneglycol, and polyethylene glycol and may be of the most important, since they are nontoxic, pharmaceutically acceptable, and nonirritant to nasal mucosa.

3. Enzymatic inhibitors

Nasal mucus layer and nasal mucosa act as enzymatic barriers during nasal drug delivery, because they have a wide variety of enzymes. Various approaches have been used to avoid enzymatic degradation, including the use of proteases and peptidases inhibitors. For example, bestatine and comostate amylase are used as aminoptidases inhibitors and leupeptine and aprotinin as trypsin inhibitors probably involved in the degradation of calcitonin. Furthermore, bacitracin, amastatin, boroleucin and puromycin (Bernkop 1998) have been used to avoid enzymatic degradation of drugs such as leucine enkephalin (Hoang, 2002) and human growth hormone (O'Hagan, 1990). Finally, enzymatic inhibition can also be achieved using certain absorption enhancers (bile salts and fusidic acid). It is demonstrated that disodium EDTA, an absorption enhancer, reduces enzymatic degradation of beta sheet breaker peptide used for the treatment of Alzheimer's disease (Greimel et al, 2007).

4. Permeation enhancers

Small and large hydrophilic drugs may be poorly permeable across nasal epithelium and may show insufficient bioavailability. Their permeation can improve by being administered in combination with absorption enhancers which induce reversible modifications on the structure of epithelial barrier. (Table -1)

Table 1: Mucosal penetration enhancers and mechanisms of action.

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

DELIVERY SYSTEM BASED APPROACHES FOR INTRANASAL DRUG DELIVERY

1. Nasal spray

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

2. Nasal drops

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

3. Nasal gels

Nasal gels are high-viscosity thickened solutions or suspensions. The advantages of a nasal gel includes the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target to mucosa for better absorption.

4. Nasal powder

This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage form are

the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particles size, aerodynamic properties and nasal irritancy of the active drug and /or excipients.

5. Liposomes

Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included. Liposomal drug delivery systems present various advantages such as the effective encapsulation of small and large molecules with a wide range of hydrophilicity and pKa values (Alsarra et al, 2008). In fact, they have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration. This has been attributed to the increasing nasal retention of peptides (Kato et al, 1993). Protection of the entrapped peptides from enzymatic degradation and mucosal membrane disruption. The results demonstrated that this formulation was effective and that its mucoadhesive property is a viable option for a sustained release of insulin. Moreover, liposomal drug delivery systems were also reported as useful for influenza vaccine and non-peptide drugs such as nifedipine (Vyas et al, 1995).

6. Nanoparticles

Nanoparticles may offer several advantages due to their small size, but only the smallest nanoparticles penetrate the mucosal membrane by paracellular route and in a limited quantity because the tight junctions are in the order of 3.9-8.4 \AA . Controversial results are found when using nanoparticles in intranasal drug delivery (Simon et al, 2005).

7. Intranasal microemulsion

Intranasal microemulsion is one of the focused delivery options for noninvasive drug delivery to systemic circulation. 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. In other studies, Vyas et al reported rapid and larger extent of drug transport into rat brain following intranasal administration of mucoadhesive microemulsions of zolmitriptan and sumatriptan. 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 risperidone. Elshafeey(2009) showed that the intranasal delivery of microemulsion of sildenafil citrate showed shorter T_{max} and higher AUC compared to the oral tablets in rabbits and higher relative bioavailability of sildenafil citrate.

8. Intranasal microspheres

Microsphere technology has been widely applied in designing formulations for nasal drug delivery. Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery. Furthermore, microspheres may also protect the drug from

enzymatic metabolism and sustain drug release, prolonging its effect. Wang et al., have investigated laminated gelatin microspheres as a nasal drug delivery system for insulin. They have observed a significant hypoglycemic effect when administered intranasally in dry powder form to rats, but no significant effect was achieved when given in a suspension. Gavine et al have analyzed nasal mucosa after its exposure to microspheres of alginate/chitosan containing metoclopramide(Gavini et al 2006). They observed open tight junctions in the epithelium and also stated that these spray-dried microspheres have promising properties as mucoadhesive nasal carriers.

APPLICATION OF NASAL DELIVERY

Intranasal administration confers a simple, economic, convenient and noninvasive route for rapid drug delivery to systemic circulation.(table-2)

1. Treatment of epilepsy and schizophrenia;
2. Treatment of migraine
3. As an antidepressant
4. Treatment of angina pectoris and neurological deficit
5. Treatment of amnesia
6. Intranasal delivery of peptides
7. Intranasal delivery of vaccine
8. Intranasal delivery of analgesics

CONCLUSION

The nasal mucosa offers several advantages for controlled drug delivery. The mucosa is well supplied with both vascular and lymphatic drainage; first-pass metabolism in the liver and pre-systemic elimination in the GI tract is avoided. The area is well suited for a retentive device and appears to be acceptable to patients. With the proper formulation and dosage form design, the permeability and the local environment of the mucosa can be controlled and manipulated to accommodate drug permeation. Nasal drug delivery is a promising area for systemic delivery of orally inefficient drugs as well as an attractive alternative for non-invasive delivery of potent peptide and perhaps protein drug molecules. The intranasal route is an accessible alternative to parenteral routes. The need for safe and effective nasal permeation and absorption enhancers is a crucial component for a promising future in the area of nasal drug delivery.

Table 2: Advantages and challenges in intranasal vaccination.

Advantages	Challenges
Easily accessible mucosal organ	Narrow nasal entrance
Highly vascularised mucosa	Complex geometry with narrow passages
Large surface available for absorption	Variable dosing with traditional delivery method
Both mucosal and systemic immune responses	Mucociliary clearance and nasal cycle
Protection at distant mucosal sites	Reformulation of vaccines required
Suitable for mass vaccination	Adjuvant required for good immune response
Needle free vaccination	Influences of nasal inflammation and obstruction

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