

Nasal Drug delivery in Pharmaceutical and biotechnology: present and future

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Abstract

For many years, drugs have been administered intranasally for their local effect on the mucosa (e.g. Antihistamines, decongestant, vasoconstrictors and antibiotics). In more recent years many drugs have been shown to achieve a better systemic bioavailability by self medication through the nasal route than by oral administration. Some of them have been shown to duplicate the plasma profile as i.v. administration. More recently the intranasal route has aroused increasing interest as means of the systemic administration of vaccine, hormones, peptides and certain other drugs. Although traditional nasal drug delivery methods offer significant advantages over injection or oral administration, they face challenges that limit efficacy and applications. Once relegated to treating conditions such as nasal congestion and rhinitis, intranasal drug delivery is now gaining attention for administration of a wide range of pharmaceuticals. Pharmaceutical industries are looking at nasal drug-delivery options as a viable alternative to traditional routes of administration for systemic drugs. This is due to the high permeability of the nasal epithelium, allowing a higher molecular mass cut-off at approximately 1000 Da, and the rapid drug absorption rate with plasma drug profiles sometimes almost identical to those from intravenous injections. In this review, discuss the history of overall nasal drug delivery in the pharmaceutical and biotech industries at present and suggestions for the future.

Key words: Nasal drug delivery, pharmaceutical and biopharmaceutical, Drug delivery, parenteral route

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Introduction

The intranasal application of tobacco stuff, cocaine, and various hallucinogenic and psychotropic agents has been known for a long time. It is therefore surprising that only in the past decade the intranasal administration of drugs for the systemic use has attracted much attention. Recent reviews¹⁻⁶ books and symposium proceedings⁷⁻⁸ Show a strongly increasing interest in nasal delivery for systemic absorption as an alternative to the parenteral route.

Historically, the use of the nasal route for drug delivery has received attention of mankind since ancient times. Nasal therapy, also called “NASAYA KARMA”, has been recognized form of treatment in the Ayurvedic systems of Indian medicine.

For many years, drugs have been administered intranasally for their local effect on the mucosa (e.g. Antihistamines, decongestant, vasoconstrictors and antibiotics). In more recent years many drugs have been shown to achieve a better systemic bioavailability by self medication through the nasal route than by oral administration. Some of them have been shown to duplicate the plasma profile as i.v. administration. More recently the intranasal route has aroused increasing interest as means of the systemic administration of vaccine, hormones, peptides and certain other drugs.

There are situations in which a systemic medication is required but the parenteral administration may be either undesirable or impractical, whereas the oral administration may not be suitable due to some potential systemic bioavailability problems associated with g.i. stability and/or hepatic first pass metabolism.

Transnasal delivery has the advantage of providing direct entry of drug into the systemic circulation, as well as ease of administration. The nasal mucosa, unlike the skin, is not constructed from the highly keratinized stratum corneum, but from numerous microvilli underlined with rich vascularity. The nasal route, therefore, appears to be ideally suitable for nonparenteral administration of drugs intended for systemic medication.

Discussion

A.1. Why nasal drug delivery?

Nasal drug delivery is a useful delivery method for drugs that are active in low doses and show no minimal 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 therapeutics 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 gastrointestinal tract, poor absorption properties, and their rapid and extensive biotransformation¹¹⁻¹³. Therefore, nasal delivery is promising alternative route for the administration of peptides and protein drugs in particular.

A.2. Advantages of nasal drug delivery system

1. Many drugs when given per orally or deep rectally undergo first pass elimination which is the biotransformation of the drug in the gut lumen prior to absorption and in the intestinal epithelium and/or liver after permeation of the intestinal mucosa (pre-systemic) but before entering systemic circulation. For such compounds g.i t. is poor choice for administration and nasal route is one of the alternatives.

2. Drugs possessing poor stability in g.i.t. fluids are given by nasal route.
3. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.
4. Provides a suitable route of administration for drugs such as peptides or proteins, which are destroyed by the gastrointestinal fluids, and not capable of being adequately absorbed into the systemic circulation following oral administration.

A.3.Limitations of nasal drug delivery systems

1. There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
2. Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
3. The common cold or any pathological conditions involving mucociliary dysfunction, can greatly affect the rate of nasal Clearance and subsequently the therapeutic efficacy of the drug administered nasally.
4. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

A.4. Anatomy and physiology of the nose:

A.4.1. Anatomy

The human skull is composed of two functional sections that protect the delicate structures within them. The neurocranium surrounds and protect the brain while the viscerocranium surrounds and protect the eyes, the mouth and the nasal cavity¹⁴. The nasal cavity is divided into two symmetrical halves by the nasal septum and extends posterior to the nasopharynx. The most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril (Fig 1). The atrium is an intermediate region between the vestibule and the respiratory region. The respiratory region, the nasal turbinates, occupies the major part of the nasal cavity. It possesses lateral walls that divide it into three sections comprising the superior nasal turbinate at the top. Below this is the middle nasal turbinate. The lowest chamber is the inferior turbinate. These folds provide the nasal cavity with a very high surface area compared with its small volume.

A.4.2. Morphology and physiology of the nose

The basic functions of the nose are heating and humidification of inspired air before it reaches the lungs, olfaction, resonance, filtration of particles, mucociliary clearance, and antimicrobial, antiviral and immunological activities¹⁵. The anatomy of the nose and functions of the epithelial cells at the different regions of the nasal cavity are such that these functions are performed optimally. The olfactory region situated above the superior nasal turbinate possesses specialized ciliated olfactory nerve cells for smell perception. The central axon of these nerve cells pass through the cribriform plate of the ethmoid and into the olfactory bulb. The total surface area of the olfactory epithelium is 200-400 mm¹⁶. The nasal vestibule, opening to the outside environment, possesses numerous nasal that filter large air borne particles.

The epithelial cells in this region are stratified, squamous and keratinised with sebaceous gland. Due to its nature, the nasal vestibule is very resistant to dehydration and can withstand against noxious substances of the environment. On the other hand, permeation of substances through it is very limited. As a result, it is not the preferred site for drug administration and absorption. The intermediate region between the nasal vestibule and nasal conchae is the atrium. This is a transitional epithelium region with stratified, squamous cells anteriorly and pseudostratified columnar epithelium with microvilli, posteriorly. Pseudostratified columnar epithelial cells interspersed with goblet cells cover the respiratory region, and also present are seromucus ducts, the opening of subepithelial seromucus glands. Furthermore, many of these cells possess actively beating cilia with microvilli. Each ciliated cells contains approximately 100 cilia, and both ciliated and non ciliated possess approximately 300 microvilli each. Also present are non-ciliated cells and basal cells. The basal cells subsequently differentiate to form other epithelial cell types and also believed to help the columnar cells adhere to the basement membrane¹⁷. collectively, the epithelium and lamina propria are called respiratory mucus membrane of respiratory mucosa¹⁸. the respiratory mucosa is the region where drug absorption is optimal. A thin sheet of Mucus produced from the seromucus glands and goblet cells covers the nasal turbinate and the atrium.

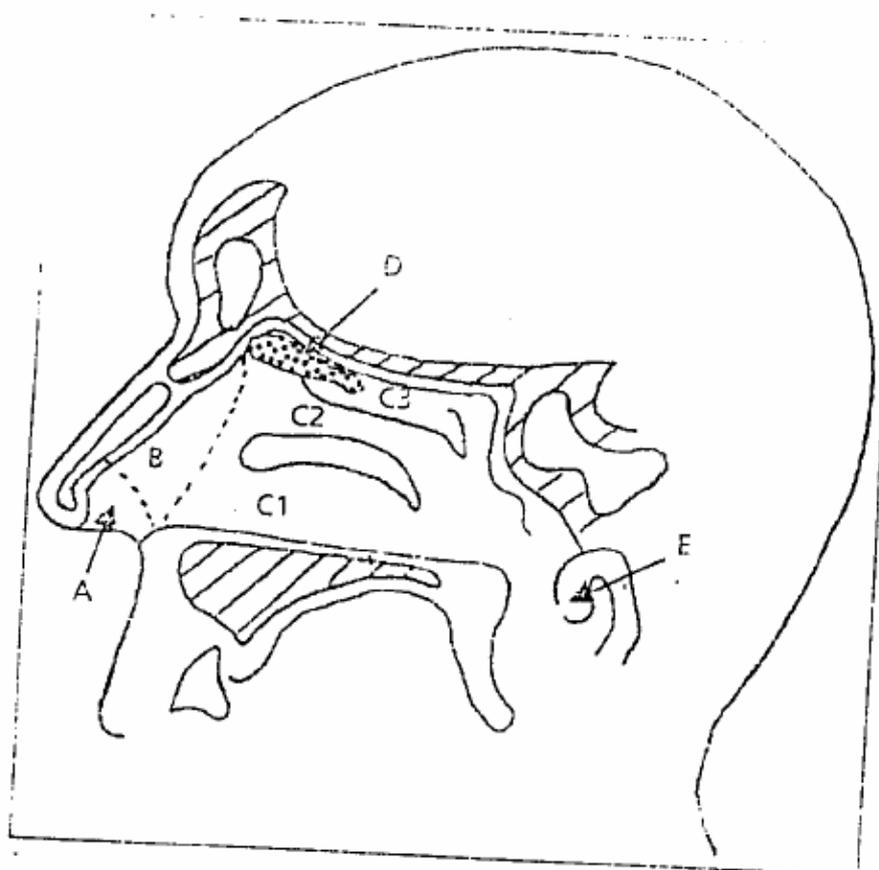


Fig. 1 Saggital section of the nasal cavity showing the nasal vestibule (A), atrium (B), respiratory area: inferior turbinate (C1), middle turbinate (C2) and superior turbinate (C3), the olfactory region (D), and nasopharynx (E)

A.4.3 Sensory innervations and nervous system control

Nasal blood supply and secretions are controlled by the autonomic nervous systems. Sensory innervations of the nasal cavity are via the ophthalmic and maxillary division of the trigeminal nerve⁷¹. The resistance vessels, located close to the surface of the nasal mucosa, are muscular vessels with narrow lumen. These vessels are predominantly under adrenergic control but also receive alpha adrenergic innervations, and provide the blood needed to heat and humidify inspired air. The capacitance vessels are thin walled and elastic, and are located deeper within the submucosa. They receive primarily alpha adrenergic innervations. The capacitance vessels are responsible for most of the blood content of the nasal mucosa.

Both parasympathetic fibers and sympathetic fibers innervate nasal secretory glands. The stimulation of parasympathetic fibers causes increased secretion that is proportional to the frequency of stimulation, and is blocked by atropine. It also slowly decreases total nasal blood flow, and this effect is not affected by atropine. Sympathetic stimulation causes a strong and rapid contraction of the resistance vessels and decreased capacitance blood flow¹⁹.

A.4.4 Nasal secretion and mucus layer

A blanket of viscoelastic fluid, the mucus, covers the respiratory part of the nasal cavity. The greater quantity of nasal mucus is secreted from the submucosal glands. These glands are composed of both mucus cells and serous cells that produce a watery fluid²⁰. There are an estimated 100000 seromucus glands in the human nose. This number is higher than in the trachea and is independent of age²¹. Mucus is also released from the goblet cells, as mucus granules. Following swelling in the nasal fluid, the mucus layer is formed. The nasal secretion is complex mixture of several materials and consists of approximately 95% water, 2% mucin, 1% of other proteins such as albumin, immunoglobulins, lysozymes and lactoferrins and less than 1% lipids²². The production of immunoglobulin A by both the adenoid tissue and the nasal mucosa plays a very important role in immune protection against bacteria and viruses²³. The mucus glycoproteins consist of a protein core with oligosaccharide side chains cross linked by disulphide bridges and hydrogen bonds. Heterogeneity exists between the cytochemical characteristics of mucus secretion from seromucus gland and goblet cells²⁴ the mucus blanket, which is approximately 5µm thick, is made of two layers, a lower sole layer and an upper gel layer. The lower layer, which bathes the cilia, is of low viscosity, whereas the upper gel layer that rests on the cilia is a high viscosity fluid. Consequently the viscosity of both layers would affect ciliary beating and the transport of overlying mucus, the mucociliary clearance (MCC). The viscosity is very sensitive to even small changes in the mucin content. A small increase in mucin causes a very large increase in mucus viscosity with a resultant prolongation of the mucociliary clearance time²⁵.

Mucin is high molecular mass (2000000-4000000 Da) glycoprotein crosslinked with disulphide bridges, ionic bonds and physical entanglements. The carbohydrate side groups attached to the protein backbone include galactose, L-fructose group, which make mucin an anionic polyelectrolyte at neutral pH. Due to the multiplicity of hydroxyl groups of the carbohydrate side chains, mucin easily forms hydrogen bonds with other suitable polymers²⁶.

The nasal mucus performs a number of physiological functions²⁷. It covers the mucosa, and physically and enzymatically protects it, it acts as adhesive and transports particulate matter towards the nasopharynx, the mucus has water holding capacity, it exhibits surface electrical activity and it permits efficient transfer.

A.4.5 Mucociliary clearance

One of the functions of the upper respiratory tract is to prevent noxious substances (allergens, bacteria, viruses, toxins etc.) from reaching the lungs. When such materials adhere to, or dissolve in, the mucus lining of the nasal cavity, they are transported towards the nasopharynx for eventual discharge into the gastrointestinal tract. Clearance of this mucus and the adsorbed/dissolved substances into the GIT is called the MCC. As the name implies, efficient MCC has contribution from both the mucus and the cilia, which is the motor of the MCC. Consequently, factors that affect either the mucus or the cilia would influence the MCC. It is of utmost importance that the MCC is not impaired in order to prevent lower respiratory tract infections. The depressant effect of anesthetics on MCC has been proposed to be the major cause of postoperative respiratory tract infections²⁸. Even though it has been estimated that the mucus transport rate is 6 mm/min²⁹ there is a wide variation in MCC between different individuals, but within one subject it is fairly constant. The concept of fast movers and slow movers is well documented. This implies that there are individuals with a very fast MCC rate and others whose MCC rate is slow. This is independent of age and sex. However, at the periovulatory period of the menstrual cycle, increased MCC occurs and was proposed to be due to the accompanying reduced mucus viscosity³⁰.

A.4.6. Factors that affect MCC

Both temporal environmental as well as disease conditions can influence MCC. All factors that can lead to increased mucus production, decreased mucus viscosity increase ciliary beat frequency (CBF) without disrupting the metachronal wave, can increase the MCC rate. The opposite effects as well as destruction of the viscoelastic properties of the mucus and disruption of the metachronal wave, reduce MCC rate.

Environmental conditions such as temperature cause a moderate reduction of the MCC rate³¹. The following pathological conditions of the upper respiratory tract influence MCC due to their effect on ciliary beating and/or mucus rheology. These include Kartagener's syndrome, sjogren's syndrome, asthma, nasal polyposis, and deviation of nasal septum, rhinitis, allergic rhinitis, common cold and chronic sinusitis.

The relevance of these disease conditions in nasal drug delivery can not be over-emphasized. Pathological conditions with increased MCC rate reduce contact time of the drug with the absorptive nasal mucosa, whereas decreased MCC rate has the opposite effect. Nasal hypersecretion dilutes nasally administered drug solutions leading to reduced concentration gradient, with a possible influence on absorption. A change in the pH of the mucus can affect the ionization of some drugs, and this can have a significant influence on nasal drug absorption.

A.4.7. Ciliary beat cycles and mechanism of ciliary beating

For the MCC to function efficiently as the first line of defense for the lungs, the cilia must beat in a well coordinated manner(both in phase and frequency), and this is called the metachronal wave. In this way a coordinated clearance towards the nasopharynx is ensured. In the small part of the anterior nares, the direction of MCC is forward, with clearance of mucus and deposited particles carried out by blowing and wiping the nose²⁷¹.

A cilium is made of an azoneme surrounded by the ciliary membrane. The azoneme itself consists of two central microbubules(A and B microbubules), and arrangement termed the 9+2 formation of microbubules(fig.2). the peripheral microtubules are connected to each other by nixing links and radial spokes connect the central microtubules, thereby giving the microbubule a rigid structure. Two dynein arms(inner and outer dynein) are attached to one of each pair of the periphery microtubules. Due to their ATPase activity, the dynein arms provide the energy required for ciliary beating³³.

Ciliary motility is generally accepted to result from the sliding movement of adjacent axonemal microtubules. The dynein arms of these microbubules provide the mechanochemistry for the movement, as a result of their ATPase activity. One theory of axonemal movement suggest that the dynein A microbubule transiently attaches to ,and detaches from, the dynein B microtubule after ATP binding and hydrolysis, causing the doublet to move to the opposite direction. Other axonemal structures resist this movement thereby causing the bending and unidirectional movement³⁴. The switch point theory hypothesizes that one set of the doublets is active during the effective stroke and the other set during the recovery phase. Activity therefore switches back and forth between the two sets causing the asynchronous and bending motion³⁵. another theory is that an electrochemical signal over the cell surface may be responsible for synchronizing ciliary beading in the metachronal wave, even though this signal is not needed in initiating the ciliary beating³⁶.

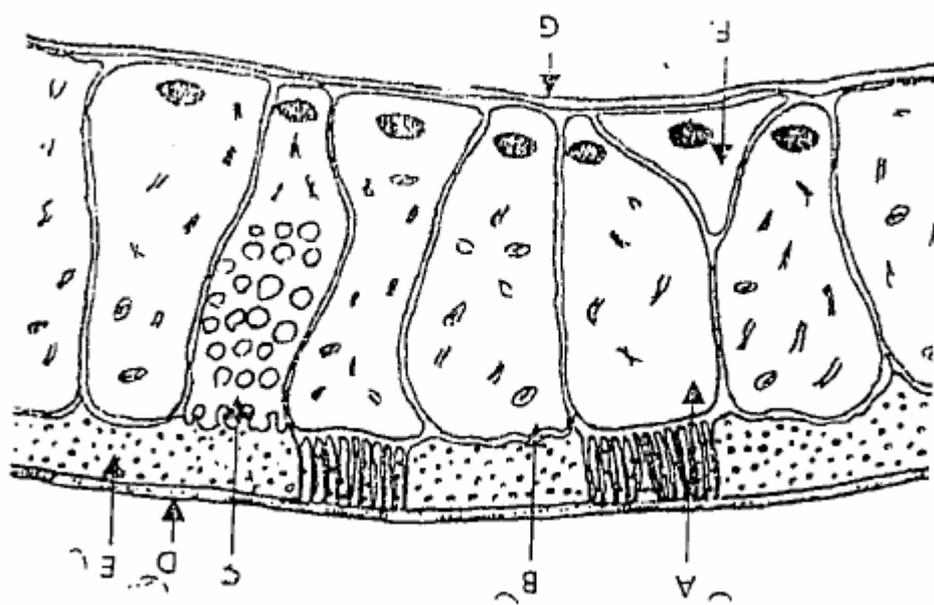


Fig.2. Cell type of the nasal epithelium showing ciliated cell (A),nonciliated cell(B), goblet cell(C), gel mucus layer(D), sol layer(E), basal cell (F), and basement membrane (G).

Ciliary beating has three identifiable phases, an active/effective phase, a rest phase and a recovery phase. During the active phase the cilium maximizes its length within the sol layer, reaching out beneath the gel mucus layer and clawing it with the tiny projections on its tip. The effective phase is followed by a rest phase when the cilium is bent and almost parallel to the cell surface. The beat cycle is completed with the recovery phase where the cilium recoils back to the initial position, ready for the next cycle. This asymmetric beating enables propulsion of the mucus in one direction. In one beat cycle each cilium makes an arc of approximately 110° . More time is spent during the rest phase than during active phases. The frequency of ciliary beating varies a lot, with a range of 10-20 Hz.

A.4.8. Experimental models used in nasal drug delivery studies

Many different models are used in nasal drug delivery research. These include *in vitro*, *in situ* and *in vivo* models. Each model has its advantages and limitations that affect how the results obtained can be interpreted and/ or extrapolated to the *in vivo* human situation. *In vitro* models are cheap and allowed rapid screening of a large number of compounds, as well as avoiding the sometimes-controversial use of animals in biomedical research. *In vivo* models are expensive and also labour intensive. Variability in the result can be introduced due to species differences in the animal used (*in vitro*, *in-situ* and *in-vivo*). A brief description of each model would be appropriate to understand nasal drug delivery experimental methodology.

A.4.9. In vitro/ ex vivo models

The advantages of *in vitro* approaches to experimental studies are largely due to the ability to control a lot of variables. Mechanistic aspects of nasal drug delivery are easier performed *in vitro*. It is also easier to separate the process of drug permeation across the epithelium from subsequent events such as biodistribution and elimination, as well as local blood flow³⁷. Other advantages of *in vitro* models used in studying nasal drug delivery include: fast assessment of the potential permeability and metabolism of a drug, rapid screening of toxicity of drugs and excipients, the opportunity to elucidate the molecular mechanisms of drug transports across the epithelium and pathways of degradation and ways of preventing such degradation, the possibility of using human tissues, and a reduction in the number of animals used at later stages of the drug development process. However, the simplistic environmental conditions are frequently different to *in vivo* situations. A number of *in vitro* models have been, and are being developed for use in nasal drug delivery studies. These include cell cultures (both human and animal primary cell cultures and cell lines) and excised tissues (*ex-vivo*) from different animal species. Three types of cell lines used in nasal drug delivery studies are RPMI 2650 (derived from cancerous human septum) BT (obtained from normal bovine turbinate) and NAS 2BL (from rat nasal squamous carcinoma)³⁸. Research with these cell lines is still at the developmental stages. BT cells do not express perijunctional complexes (tight junctions) but rather expressed stress fibers basolaterally to enhance cell attachment. RPMI 2650 expressed tight junctions but without achieving confluency³⁹. Although metabolic studies can be performed with these cell lines, their characteristics need further improvement before use in transport and metabolic studies, have been reported⁴⁰. *Ex vivo* models use materials from different animal species. The excised tissues can be mounted in using chambers for performing both transport and metabolic studies.

A.4.10. In situ models

This method involves perfusing a drug solution through nasal cavity of an experimental animal and monitoring absorption results, which are difficult to compare with other animal species or even to extrapolate to the human situation.

The mouse is largely used in the intranasal immunization and toxicity studies. Pharmacokinetic studies are limited due its small size, and consequently the small total blood volume. The respiratory epithelium is composed of pseudostratified columnar epithelium that is ciliated. The percentage of mouse nasal cavity covered by squamous, pseudostratified columnar and olfactory epithelium are 7, 46 and 47% respectively. For nasal toxicity experiments, mice can not be used as intra animal controls because of the existence of the septal window. This connects the two nasal cavities and allows inter cavity migration of substances under study⁴¹.

The nasal cavity of rats has three regions of distinct epithelial types: squamous, pseudostratified columnar and olfactory epithelium. The relative proportion of the total surface area of the nasal cavity they cover are 3,47 and 50% respectively, which is similar to that of mouse. The nasal septal window is also present, with the aforementioned disadvantages. Furthermore location of the nasopalantine tract, anteriorly in the nasal cavity, has consequence that nasally administered drug solution can easily drain into the oral cavity. It is important to close the palatine during drug absorption studies⁴². the orifice(entrance of the rat nose is restricted(table 1) such that drug administration could be difficult, especially for powder formulations.

The advantages favoring the use of rat in nasal drug delivery studies are ready availability and low unit cost.

The guinea pig is also used mostly for immunization studies. The septal window is also present, and squamous epithelium covers a large part of the vestibule such that drugs have to be applied deep into the nasal cavity⁴³.

The use of rabbits offers a number of advantages. They are suitable for both pharmacokinetics and pharmacodynamic studies. Additionally, repeated experiments can be performed on the same animal after an appropriate drug washout and recovery period. This would reduce both the total cost of experiments and variability in the data. The large entrance into the nasal cavity(orifice compared with rats enables easy administration of both drug solutions and powders. Pharmacokinetics experiments can be performed without the need for the anesthesia, especially since some anesthetics can inhibit MCC⁴⁴, which would affect nasal drug absorption. Other advantages include the relative cheap price, easy availability, maintenance and handling. The large total blood volume(approx. 300ml) can allow repeated blood sampling. The branching nasal septum of rabbits is anatomically similar to dogs. The respiratory mucosa is pseudostratified and columnar ciliated epithelium with goblet cells.

The sheep presents a nasal cavity with surface area and volume that is even larger that of man. Its docile nature, which facilitates easy intranasal administration, is a major advantage. Pharmacokinetics and pharmacodynamic studies can be repeatedly performed on it without anesthesia. It is however more expensive than smaller animals such as rabbits and rats. During warm weather conditions, the insulation provided by the wool prevents evaporation of sweat from the skin. The

nasal cavity provides the route for sweat evaporation under such conditions. This could influence nasal drug absorption, especially of drugs transported across the epithelium via passive paracellular transport. This calls for proper housing conditions during experiments⁴⁵.

Dogs can also be used easily without anesthesia in nasal drug delivery studies. Both pharmacokinetics and pharmacodynamic studies are also possible, and can be repeated on the same animal. Some breeds of dog are easy to handle during intranasal administration. The large nasal cavity is very interesting but cost is a major limitation. Cost consideration rule out the routine use of sheep and dogs, but not rabbits for nasal toxicity studies.

The only advantage of using monkeys in drug research in general is that they are primates. However, they are very expensive and their use in medical research is strongly protested against by animal rights groups. While the use of animals in medical research continues to be necessary, the choice of which animal to be used depends on the study in question. For nasal drug delivery purposes, small laboratory animals (mice, rats, and guinea pigs) are very useful for toxicity studies due to their cheap price. Large animals (dogs and sheep) can be used repeatedly for pharmacokinetics and pharmacodynamics studies. Rabbits can be used conveniently for both types of experiments.

A.4.11. Pathways for nasal absorption

The process of transport across the nasal membrane involves either the diffusion of drug molecules through the pores in the nasal mucosa or participation of some non-passive pathways before they reach the blood stream⁴⁶. In addition, the olfactory epithelium is known to be a portal for substance to enter the central nervous system (CNS) and the peripheral circulation. However, the mechanism of transport still remains unknown.

The potential pathways involved in the nasal absorption of some drugs reported in literature are summarized in Table 1

SUBSTANCE	POSSIBLE PATHEAYS
Dopamine ⁴⁷	Nasal mucus membrane- CSF and serum (detected within 15 minutes after administration)
Estradiol ⁴⁸	Nasal membrane-CSF (Within 1 minute)
Progesteron ⁴⁹	Nasal membrane- olfactory dendrites- nervous system supporting cell in olfactory mucosa – submucosal blood vascular system –CSF(within 1 minute)
Lead carbonate ⁵⁰	Dissolved in nasal mucus and then absorbed as true solution
Chloride salt ⁵¹	Nasal membrane- blood circulation.
Distilled water	Nasopharynx-cervical lymph.

A.4.12. Pharmacokinetics of nasal absorption

Factors reported to affect the pharmacokinetics parameters following intranasal administration^{52,53} are,

1. Physiological related factors such as
 - a) Speed of mucus flow
 - b) Presence of infection
 - c) Atmospheric conditions
2. Dosage form related factors such as
 - a) Concentration of active drug
 - b) Physicochemical properties of active drug
 - c) Density/viscosity of formulation
 - d) pH/toxicity of dosage form
 - e) Pharmaceutical excipients
3. Administration related factors, such as
 - a) Size of droplets
 - b) Site of deposition
 - c) Mechanical loss into the esophagus
 - d) Mechanical loss to other regions in the nose
 - e) Mechanical loss anteriorly from nose

The bioavailability of drug after intranasal administration may be expressed in terms of absolute absorption, AC determined from the area under curve (AUC) following the intravenous (i.v.) and intranasal(I.N.) dose.

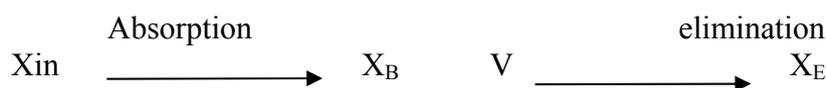
$$AC = \frac{(AUC) \text{ I.N (DOSE) I.V}}{(AUC)} \quad 1$$

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)

$$AC = \frac{(AU_2) \text{ I.N (DOSE) I.V.}}{(AU_2)} \quad 2$$

Equation 2 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 :



X_{in} - amount of drug administered to the nasal site.

X_B - amount of drug in central compartment

V - apparent volume of distribution

X_E - amount of drug eliminated

A.4.13. Factors influencing nasal drug absorption

The rate and extent of nasal absorption of a drug is dependent upon lipophilicity, molecular weight, environment pH, and stability to enzyme degradation.

A. Lipophilicity

The rate and extent of absorption of drug across biological membrane are often influenced by its lipophilicity. The effect of lipophilicity on the extent of nasal absorption was studied using series of barbiturates at pH 6, at which barbiturates ($pK_a=7.6$) exists entirely in the nonionised form²⁹³.

B. Environmental pH

The environmental pH plays an important role in the efficiency of nasal drug absorption. Studies of several small water-soluble compounds such as benzoic acid, salicylic acid, and alkaloid acid show that their nasal absorption in rat occurred to the greatest extent at those pH values where these compounds are in the nonionised form. However, at pH values where these compounds are partially ionized, substantial absorption was found. This means that the nonionised lipophilic form crosses the nasal epithelial barrier via transcellular route, whereas the more lipophilic ionized form passes through the aqueous paracellular route.

Using a number of water soluble and macromolecular marketed compounds, such as polyethylene glycol, and fluorescein isothiocyanate (FITC), diethylaminoethyl (DEAE), and DIT labeled dextrans, ranging in size from 600 to 70,000 Dalton, a reverse relationship has been demonstrated between molecular size and nasal absorption in rats and rabbits⁷².

These studies support the ideal that water-soluble high molecular weight drugs cross the nasal mucosa mainly by passive diffusion through the aqueous pores (i.e. tight junctions).

A.4.14. Enhancement of nasal drug absorption

Several methods have been used to facilitate the nasal absorption of drugs:

1. Structural modification

The chemical modification of drug molecule has been commonly used to modify the physicochemical properties of a drug and could also be utilized to improve the nasal absorption of drug.

2. Salt or ester formation

The drug could be converted to form a salt or ester for a better trans-nasal permeability. For example, nasal absorption could be improved significantly by forming a salt with increased solubility in nasal fluid (Table 2) or ester with the enhanced uptake by nasal epithelium⁵⁴.

2. Formulation design

Proper selection of pharmaceutical excipients in development of nasal formulation could enhance the formulation stability and/or the nasal bioavailability of drug.

3. Surfactant

Incorporation of proper surfactants into nasal dosage forms could modify the permeability of nasal membrane, which may facilitate the nasal absorption of drugs Table 2 below summarized the surfactant used in nasal drug delivery.

Table 2. Absorption enhancers used in nasal drug delivery⁵⁴⁻⁵⁸

CLASS	COMPOUND
Surfactants	Polyoxyethylene-9-lauryl ether (Laureth-9): Saponin
Bile salts	Trihydroxy salts (glycol- and taurocholate) Fusidic acid derivatives (STDHF)
Chelators	Salicylates Ethylenediaminetetraacetic acid (EDTA)
Fatty acid salts	Oleic acid Caprylate (C8) Caprate (C10) Laurate (C12)
phospholipids	Lysophosphatidylcholine (lyso-PC) Didecanoyl – PC
Glycyrrhetic acid derivatives	Carbenzoline Glycyrrhizinate
Cyclodextrins	α , β , and γ - cyclodextrins and their derivatives
Glycols	n- glycofurols n- ethylene glycols

A.4.15. Drug distribution in nasal cavity

The drug distribution in the nasal cavity is one of the important factors, which affect the efficiency of nasal absorption. 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. Using a cast of human nose, it was demonstrated that a significant difference in drug distribution was observed by comparing

different types of nasal delivery systems, like nose drop, plastic bottle, nebulizer, atomized pump and metered dose pressurized aerosols⁵⁹⁻⁶⁰. The result indicated that atomized pump is the best nasal delivery system because it gives constant dose and very good mucosal distribution. The result also suggests that the use of a large volume of a weak solution is preferable to small volume of concentrated solution. This may be particularly important when vasoconstrictor is used locally⁶¹.

A.4.16. Delivery systems for intranasal drug administration

There are several types of drug delivery system, which have been long used for the delivery of drug to nasal cavity, such as nasal spray, nose drops, saturated cotton pledge, aerosol spray and insufflators. Table 3 given lists the drugs that have been administered intranasally for systemic medication and type of drug delivery devices used.

Table 3. Delivery means and devices for intranasal administration of drugs⁶².

DRUGS	DELIVERY DEVICES
Adrenal corticosteroids jelly	Nasal spray, nasal drops, nasal insufflators, submucosal injections into the anterior tip of inferior turbine, metered dose aerosol
Antihistaminics	Nasal spray, nasal drops
Buserelin Formulations	Nasal spray, ointment
Calcitonin	Nose drops
Cocaine	Nasal spray, nose drops, cotton pledget, gauge packtail, insufflators, rubbing with cocaine mud
Dopamine	Nasal spray
Estradiol- 17β	Nasal spray, nasal drops, microsyringe
Gentaminin	Nasal spray
Hyoscine(scopolamine	Nasal spray, nasal drops
Insulin	Metered pump sprayer, metered dose aerosolized spray, fixed volume aerosol spray, nasal spray, nasal drops, cotton pledget
Isosorbide dinitrate	Nasal spray(iso mack spray
Naferelein acetate	Nasal spray, tobacco snuff, injected into dogs frontal sinus
Nitroglycerin	Metered dose spray Instilled through Teflon i.v. Catheter
Oxytocin	Nasal spray, nasal drops, cotton pleadget, aerosol activated spray, rhynyl (a plastic application tube), graded polyethylene tube,direct instillation by tuberculin syringe and 25G needle
Progesterone	Nasal spray by an atomizer connected to a respiratory pump, nasal spray by gas atomizer, nasal solution administered by micropipette
Vaccines	Inhalation aerosol, nasal spray, nasal aerosol spray, nebulizer aerosol, nasal drops
Vitamin B12	Nose drops, insufflators
Xylometazoline	Nasal spray, nose drops

A.4.17. Intranasal delivery of non peptide drugs⁶³

Drugs with the extensive “first pass” metabolism such as progesterone, estradiol, testosterone, hydralazine, propranolol, and nitroglycerine can be rapidly absorbed through the nasal mucosa with the systemic bioavailability of approximately 100%

Some systemic bioavailability of approximately 100%

Some of nonpeptide drugs being studied for nasal delivery and have shown good bioavailability by this route includes:

- 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
 - e. Prostaglandins
- 6) Central nervous systems stimulants: cocaine, lidocaine
- 7) Narcotics and antagonists: bupemorphine, naloxane
- 8) Histamine and antihistamines: disodium cromoglycate, meclizine
- 9) Antimigrane drugs: dierogotamine,ergotamine,tartarate
- 10) Phenicillin, cephalosporins, gentamycin
- 11) Antivirals : Phenyl-p-guanidine benzoate, enviroxime.
- 12) Inorganic compounds: Inorganis salts, colloidal gold, colloidal carbon, colloidal silver, Lead carbonate, and thorium B

A.4.18. Toxicological evaluations

The toxicity of nasal absorption enhancers has been estimated in recent years by measuring their effect on mucociliary transport rate, nasal morphology, ciliary beat frequency⁶⁴⁻⁶⁸.

a) Mucoliliary rate

Potential toxicities of some absorption enhancers have been tested on frog plate model, measuring the mucociliary transport after and before application of an absorption enhancers containing formulation.

b) Morphology

Several research groups have been investigating the histological effect of absorption enhancers in human tissue particularly sodium laurylsulphate, laureth-9, STDHF and LPC. With different contact times with the nasal

epithelium all these enhancers reported to cause more or less severe epithelium disruption.

c) Ciliary beat frequency

Ciliary beating is the most important parameter in nasal mucociliary clearance. It should not be hampered by nasally administered drugs and additives such as preservatives and absorption enhancers. For example, the ciliotoxic effect of 0.1% propranolol makes this drug unsuitable for chronic nasal administration⁶⁹.

The in vivo effects of variety of widely used absorption enhancers on ciliary movement have been studied by measuring the reduction of ciliary beat frequency(CBF) by these enhancers, using chicken embryo tracheal tissue and human adenoid tissue^{16,17}. the results for the bile salts, STDHF, CPC Laureth-9 and cyclodextrins are listed in table 4,5,6.

Table 4. Bile salts and effect of ciliary beat frequency

Compound	Percent (w/v)	Time(min)						N 20	species 30
		10	20	30	40	50	10		
C	1.3	20	0	0	C	1.3	20	0	0
GC	1.5	58	0	0	GC	1.5	58	0	0
GC	1.0	91	91	79	GC	1.0	91	91	79
GC	0.3	89	87	88	GC	0.3	89	87	88
TC	1.3	71	18	0	TC	1.3	71	18	0
TC	0.3	96	93	90	TC	0.3	96	93	90
TC	0.4	79	79	54	TC	0.4	79	79	54
DC	0.2	0	0	0	DC	0.2	0	0	0
DC	0.3	2	0	0	DC	0.3	2	0	0
GDC	0.2	37	5	0	GDC	0.2	37	5	0
TDC	0.2	70	21	3	TDC	0.2	70	21	3

Key: C= cholate, GC= glychocolate, TC= taurocholate, DC= deoxycholate, GDC= glycodeoxycholate, TDC= taurodeoxycholate, n.m.=not measured, ch = chicken, trachea, h=human adenoid, data are presented as mean percentages of initial frequencies (t₀=100%)

Table 5. Effect of ciliary beat frequency of STDHF, LPC and laureth-9

Compound	Percent (w/v)	Time(min)						N	species
		10	20	30	40	50	60		
STDHF	0.2	101	70	52	40	15	13	8	Ch
STDHF	0.2	101	70	52	40	15	13	8	Ch
STDHF	0.3	56	34	0	0	0	0	4	Ch
STDHF	0.3	86	82	64	39	16	0	8	Ch
STDHF	0.5-1.0	0	0	0	0	0	0	4	H
STDHF	0.5-1.0	0	0	0	0	0	0	4	h
LPC	0.5-1.0	0	0	0	0	0	0	4	Ch
Laureth-9	0.3-1.0	0	0	0	0	0	0	8	Ch

Key : STDHF = sodium taurodihydrofusidate, LPG= L- α lysophosphatidylcholine, ch= chicken trachea, h= human adenoid.

Data are presented as mean percentages of the initial frequencies ($t_0=100\%$)

Table 6. Effect of cyclodextrins on ciliary beat frequencies

Compound	Percent (w/v)	Time(min)						N	species
		10	20	30	40	50	60		
α -CD	5	35	17	7	1	0	0	4	ch
B-CD	1.8	77	81	70	71	62	63	4	ch
Γ -CD	5	72	66	70	72	70	77	4	ch
HP β CD	1	65	68	77	81	78	78	4	ch
DM β CD	2	78	76	75	72	70	72	4	ch
DM β CD	3	96	93	77	52	37	27	9	ch
DM β CD	4	71	40	30	6	5	4	4	ch
DM β CD	5	64	35	17	8	1	0	4	ch
DM β CD	2	48	22	1	0	0	0	4	ch
DM β CD	2	82	78	67	53	36	42	5	h
DM β CD	5	70	39	41	36	11	7	5	h

Key: HP β CD= hydroxypropyl- β -cyclodextrin, DM β CD= dimethyl- β -cyclodextrin, ch= chicken trachea, h= human adenoid.

Data are presented as mean percentages of the initial frequencies ($t_0=100\%$).

Conclusion

The scientific community has reached a new stage of nasal drug delivery. The nasal drug delivery is a promising alternative to injectables route of administration. It is very likely that in the near future more drugs will come in the market intended for systemic absorption in the form of nasal formulation. Several formulation factors will influence the development of a drug with a drug delivery system, On a longer term, novel nasal products for treatment of long illnesses such as diabetes, growth deficiency, osteoporosis, fertility treatment and endometriosis are also expected to be marketed.

Satish et al (2008) advised that the bioavailability of nasal drug products is one of the major challenges for pharmaceutical companies to bring their product in market. The circumstances, which do not favor clinical applicability of nasal drug product is the lack of enough basic research in the area of nasal drug delivery. In contrast, pharmaceutical companies are investing a huge amount of money in the development of nasal drug products because of growing demand of nasal drug products in global pharmaceutical market. This research environment will lead to serious of adverse effects in the society in future. To avoid such backdrops, biomedical scientists, formulation researchers, pharmaceutical companies, funding agencies, and government along with regulatory bodies should pay attention to basic research in nasal drug delivery such as nasal pathophysiology, invention of new excipients to improve the nasal bioavailability, drug delivery devices, toxicodynamic studies of drugs and excipients and *in vitro* methods for nasal drug metabolism and bioavailability.

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