Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Pharmacia Sinica, 2011, 2 (3): 94-106

Der Pharmacia Sinica

ISSN: 0976-8688
CODEN (USA): PSHIBD

Nasal drug delivery: An approach of drug delivery through nasal route

Sanjay Dey[1]*, Beduin Mahanti[1], Bhasakar Mazumder[2], Ananya Malgope[3] and Sandeepan Dasgupta[2]

[1]Bengal College of Pharmaceutical Sciences and Research, S.S.B. Sarani, Bidhannagar, Dugapur, West-Bengal, India
[2]Department of Pharmaceutical Sciences, Dibrugarh Univeristy, Dibrugarh, Assam, India
[3]Royal College of Pharmacy and Health Sciences, Andhapasara Road, Berhampur, Ganjam, Orissa, India

---

ABSTRACT

Over the last few decades transmucosal nasal drug delivery as a non-invasive route has occupied an important place in the field of drug delivery technology. This is due to high vascularity, large surface area, the avoidance of hepatic first-pass metabolism, gut wall metabolism and/or destruction in gastrointestinal tract. Since nasal mucosa offer several benefits for target drug delivery, a wide variety of therapeutic compounds may be administered intranasally for topical, systemic and central nervous system action. In this review, we focus on the different aspects of nasal anatomy, and histology, and the different factors that must be considered during the development of formulation for nasal delivery. We also outlined the different methods has been used to study the nasal absorption in rats.

Keywords: Anatomy, Physicochemical properties, Nasal products, In-situ method, in-vivo method.

INTRODUCTION

Oral route is the most desirable and convenient method of drug administration as their ease of manufacture and administration. Failure of adequate absorption through the gastrointestinal tract led to research on alternate routes of drug delivery. Researchers developed the parenteral route of drug administration to solve the above problem. For the past few decades, the transdermal route has been selected for delivery of certain drugs. However, its use is limited due to low permeability of the skin to many drugs.

Now a day, researchers have been on selected nasal mucosa as an alternate route to achieve faster and higher drug absorption. Knowledge of the nasal mucosa's high permeability and use of the nasal route for drug administration can be traced to ancient times. Realization of the nasal mucosa as a therapeutically viable alternate route came in the last two decades.

The development of suitable nasal drug delivery system is still the challenges of researchers. A better knowledge on the properties of drug molecules, formulation matrices, the nasal mucosa itself and the drug delivery systems affect drug absorption through the nasal route, is invaluable. A stable, safe and effective nasal product can be developed through appropriate and adequate preformulation studies of drug.

In the last few years, the nasal route has received a great deal of attention as a convenient and reliable method for the systemic administration of drugs, especially those which are ineffective orally and must be administered by injection.

From extensive literature search, it can be considered that the nasal delivery is suitable for drugs with the following criteria:

- ineffective orally
- used chronically
- used in small doses
- rapid entry to the general circulation is desirable.

Advantages and drawback of nasal drug delivery

Advantages of nasal drug delivery

The major advantages associated with nasal drug deliver include:

- rapid absorption, higher bioavailability, therefore, lower doses;
- fast onset of therapeutic action;
- avoidance of liver first pass metabolism;
- avoidance of metabolism by the gastrointestinal tract;
- avoidance of irritation of the gastrointestinal membrane;
- reduced risk of overdose;
- non-invasive, therefore, reduced risk of infectious disease transmission;
- ease of convenience and self-medication;
- improved patient compliance;
- can be a beneficial adjunct product to an existing product;

Drawback of nasal drug delivery

However, besides its so many advantages there is also few drawback of nasal drug delivery system. The drawbacks of nasal drug delivery include:

- mucociliary clearance reduces the residence time of drug;
- not applicable to all drugs;
- insufficient absorption due to lack of adequate aqueous solubility;
- require high volume of dose (25-200 ml) depending on aqueous solubility of drug;

- few drugs can cause nasal irritation;
- few drugs may undergo metabolic degradation in the nasal cavity;
- less suitable for chronically administered drugs;
- drugs requiring sustained blood levels should not be considered for nasal delivery as there is no conventional way of formulating sustained release type nasal dosage forms.

Anatomy of the nose

The total surface area of human nasal cavities is about 150 cm^2 and the total volume is about 15 ml. The nasal cavity is divided into two halves by the nasal septum. The volume of each cavity is approximately 7.5 ml, having a surface area around 75 cm^2. The anatomy and histology of the nasal cavity is shown in Fig. 1. The nasal cavity consists following three main regions:

The vestibular region

It is located at the opening of nasal passages and is mainly responsible for restricting entry of air borne particles. It is considered to be less important of the three regions with regard to drug absorption.

The respiratory region

The respiratory region is the largest having the highest degree of vascularity. The respiratory region contains three nasal turbinates: superior, middle, and inferior which project from the lateral wall of each of the nasal cavity. The presence of these turbinates creates a turbulent airflow through the nasal passages ensuring a better contact between the inhaled air and the mucosal surface. The respiratory region is considered as the major site for drug absorption into systemic circulation. The mucosa consists of an epithelium resting on a basement membrane and a lamina propria. The anterior part of respiratory region is covered with squamous epithelium, while he posterior part covered by a pseudostratified columnar epithelium. The cells of respiratory epithelium are covered by about 300 microvilli per cells.

The respiratory epithelium consists of four dominated cell types; ciliated columnar cells, non-ciliated columnar cells, goblet cells, and basal cells. The basal cells are situated on the basal membrane and do not extend to the apical epithelium surface, as do the other three cell types. The presence of tight junction between neighboring epithelial cells prevents the free diffusion of hydrophilic molecules across the epithelial by the paracellular route.

The olfactory region

The olfactory region is situated between the nasal septum and the lateral walls of each of the two nasal cavities and just below the cribriform plate of the ethmoid bone separating the cranial cavity from nasal cavity. The olfactory epithelium is a pseudostratified epithelium, comprising olfactory sensory neurons and two types of cells; basal cells that are able to differentiate neuronal receptor cells and sustentacular cells (supporting cell) that provide mechanical support by ensheathing neuronal receptor cells and maintain the normal extracellular potassium level for neuronal activity [1]. The olfactory epithelium is covered by a dense and viscous layer of mucus, which is secreted from the tubuloalveolar Bowman's glands and the supporting cells. The olfactory epithelium constitutes only about 5% of the total area of the nasal cavity in man [2]. It is about 10 cm^2 in surface area, and it plays a vital role in drug delivery because it bypasses the BBB, delivering therapeutic drugs to CNS [3].

It should be noted that the blood supply to the nasal mucosa is pertinent with regards to systemic drug delivery. The arterial blood supply to the nasal cavity is derived from both the external and internal carotid arteries. The blood that is supplied to olfactory region by anterior and posterior ethmoidal branches come from the ophthalmic artery supply, which is branch of carotid artery. These vessels supply the anterior portion of the nose. When the drug is administered intranasally, it can enter into the brain via three different paths [4]. The first one is the systemic pathway by which the drug is absorbed into the systemic circulation and subsequently reaches the brain by crossing BBB (especially lipophilic drug). The others are the olfactory region and the trigeminal neural pathway by which drug is transported directly from the nasal cavity to CNS (cerebrospinal fluid and brain tissue) [5]. The trigeminal nerve receptors which are present in the nasal cavity are responsible for most chemoperception and are suggested to transport the drug directly to CNS of drugs to the brain and the CNS [6].

The deep and superfacila cervical lymph nodes were of special interest in intranasal drug delivery because they are known to receive lymphatic afferents from portions of the nasal passages and nasolabial areas, respectivey [7]. This pathway is thought to mediate the efflux of large molecules and/or immune cells from sites within the CNS to the lymphatic system [8]. The connection between the brain and nasal lymphatics may offer a direct pathway from the brain interstitial fluid to the nasal submucosa that excludes direct conact with the cerebrospinal fluid [9].

There are different mechanism by which the drugs across the olfactory membrane to reach CNS. The first mechanism involves direct transfer of the drug to primary neurons of the olfactory epithelium and transport to the olfactory bulb by intracellular axonal transport with subsequent possible distribution into more distant brain tissues. The second mechanism depends on the drug permeation across the olfactory sustentacular epithelial cells, either by transcellular or paracellular mechanisms followed by uptake into CNS. The last one employs pinocytosis by olfactory neurons [2]. The drug can cross olfactory lobe by one or combination of pathways.

Physicochemical properties of drugs which affect their nasal delivery

Drug molecular weight and size

The permeation of drugs having molecular weight less than 300 Da is not significantly influenced by the physicochemical properties of the drug as they will mostly permeate hrough aqueous channels of the membrane. On the other hand, the rate of permeation is highly sensitive to molecular weight for compounds more than 300 Da [10]. The bioavailability of intranasally administered peptides and proteins including insulin may be low because of high molecular weight and hydrophilicity [11].

Drug solubility and dissolution rate

Like other routes of administration, the nasal absorption can take place only after the drug's dissolution. The dissolution rate is important in determining nasal absorption of powder and suspensions dosage forms. Rapid dissolution is very crucial for the drug particles after nasal administration otherwise the particles will be subjected to rapid clearance from the airway with subsequent reduction of the bioavailability [12].

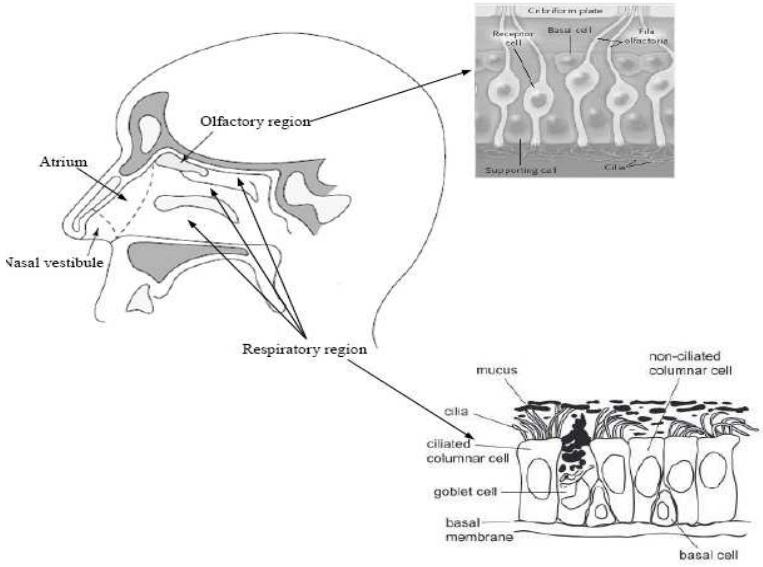

Fig. 1. Anatomy and histology of human nasal cavity (Pires et al, 2009)

pKa and the partition coefficient of drug

The nasal membrane is predominantly lipophilic, hence, the rate and extent of absorption of a drug across a biological membrane is influenced by its lipophilicity. Normally, the permeation of the compound through nasal mucosa increases with increasing lipophilicity [13]. Low molecular weight lipophilic drugs are absorbed quite efficiently across the nasal epithelium, whereas larger hydrophilic drugs, such as peptides and proteins, have substantially lower bioavailability because they are not easily transported across nasal membrane thereby enhancing mucociliary clearance. However, if lipophilicity is too high, the drug does not dissolve easily in the aqueous environment of nasal cavity, hence, with accelerated mucociliary clearance the contact time with nasal membrane diminishes resulting in a reduced permeation through the wall [14].

In general, the passage across biomembrane is affected not only by lipophilicity/hydrophilicity, but also by the amount of drug existing as uncharged species. This depends on the drug pK_a and the pH of the absorption site. According to pH partition theory, the non-ionized fraction of a drug is more permeable than that ionized. The nasal absorption of week electrolytes depends on their ionization degree and the largest absorption occurs for the non-ionized species. For polar drugs partition coefficient is the major factor influencing the permeability through nasal mucosa.

Chemical state: prodrugs

The chemical form in which a drug is presented at the nasal mucosa can be important in determining its absorption. If a drug does not have the desired absorption properties, several options can be considered to improve the drug's delivery. Prodrug technique has been employed to increase the lipophilicity. The aliphatic prodrug of acyclovir provides a classical example of this process, which resulted in an increased drug bioavailability. However, it should be noted that the 140-fold increase in partition coefficient of the drug was only associated with 30% increase in bioavailability. It should also be emphasized that the ester form of the prodrug can show

greater increase in transnasal drug transport but premature hydrolysis of such ester in the nasal cavity provides the main limitation of this technique [15].

Water-soluble prodrugs of 17β-estradiol have been evaluated after intranasal administration. These prodrugs were capable of producing high levels of estradiol in the cerebrospinal fluid (CSF), compared to an equivalent intravenous dose. These data suggest that the drug can reach the CSF via a direct pathway through the nasal cavity and as a result may have a significant value in the treatment of Alzheimer's disease [16].

Physical state: particle size and morphology

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

Polymorphism

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

Formulation properties which affect nasal drug delivery

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

Types of dosage forms and delivery systems

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

Drug concentration, dose and volume of administration

There should be clear positive relationship between absorption and drug concentration upto a certain level. Such a relationship is not always observed. There are many other confounding factors which can influence the nasal membrane transport mechanism and provide a modified absorption profile.

In general, higher nasal absorption or therapeutic effect was observed with increasing dose. It is important to note how the dose is varied. If the dose is increased by increasing formulation volume, there may be a limit as to what extent nasal absorption can be increased. The nostrils can remain only a limited volume, beyond which a formulation will drain out of the nasal cavity. The ideal dose volume range is 0.05-0.15 ml with an upper limit of 0.20 ml.

Physical form of formulation
Nasal drug absorption depends on the physical form of the formulation. A powder form was found to be more effective than liquid formulations because powder is not readily washed out with the nasal secretions.

Viscosity
As formulation viscosity increases, the contact time between drug and nasal mucosa enhances and, thereby, the potential of drug absorption increases. At the same time, high viscosity of formulations interferes with normal ciliary beating and/or mucociliary and, thus, incrases the permeability of drugs. This has been observed during nasal delivery of insulin [17], acyclovir ([18] and metoprolol [19]. However, sometimes, enhancing formulation viscosity does not enhance the drug absorption. Generally, a more viscous formulation will provide less efficient systemic nasal drug delivery. Zaki et al. [20] studied the influence of formulation viscosity on the retention time of mwtoclopramide hydrochloride in nasal cavity and on its absorption. They observed that although the residence time enhanced as viscosity increased the drug absorption diminished. This observation has been attributed to a decrease in the drug diffusion from the formulation. On the other hand, it has also been reported that the viscosity of the solution may provide a larger therapeutic period of nasal formulations [20].

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

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

To avoid nasal irritation, formulation pH should be adjusted between 4.5 and 6.5. The nasal surface pH is 7.39 and the pH of nasal secretions is 5.5-6.5 in adults and 5.0-6.7 in infants and children. The physiological properties of drugs should be kept in mind in deciding on formulation pH. Most drugs are absorbed well in their un-ionized form. While it is desirable keep the formulation pH between 4.5 and 6.5, at times a pH lower than 4.5 may have to be chosen to keep an appreciable drug fraction in the un-ionized form.

Formulation osmolarity
In a series of three articles, Ohwaki et al. [21] studied the effects of osmolarity, among other factors, on the nasal absorption of secretin in rats. They found that the absorption was affected by the concentration of sodium chloride in the formulation and the absorption reached a maximum at a 0.462 M sodium chloride concentration. Shrinkage of epithelial cells of the nasal mucosa

was observed at this salt concentration. At a formulation pH of about 3, the observed effects may have been a combination effect of the low pH and the salt concentration. Vora et al. [22] have also reported that drug absorption through the nasal mucosa can be substantially affected by formulation tonicity.

Formulation excipients

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

Biological factors which affect nasal drug absorption

Nasal blood flow

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

The blood vessels in the nasal mucosa are surrounded by adrenergic nerves which act as alpha adrenoceptors. Stimulation of these receptors has been shown to decrease blood flow and blood content in the nose of animals [23] and humans [24]. The nasal blood is affected by several external and physiological factors such as ambient temperature, humidity, presence of vasoactive drugs, trauma, and inflammation [25] as well as psychological factors such as emotion, fear, anxiety, and frustration [26].

The nasal flow is sensitive to different locally or systemically acting drugs. Drugs such as oxymetazoline [24] and clonidine [27] decrease blood flow whereas histamine [28], albuterol [29], isoproterenol [30], phenylephrine [29] and fenoterol [31] are shown to increase the blood flow. Such effects are important in determining nasal drug absorption due to their effect on blood flow.

Enzymatic activity in the nose

Drugs nasally administered circumvent gastrointestinal and hepatic first-pass effect. However, they may be significantly metabolized in lumen of nasal cavity or during the passage across the nasal epithelial barrier due to the presence of cytochrome P450 dependent monoxygenase, lactate dehydrogenase, oxidoreductase, hydrolases, acid phosphatase and esterase. It has been reported that cytochrome P450 isoenzymes metabolized the drug such as cocaine, nicotine, alcohols, progesterone and decongestants [32]. Similarly, proteolytic enzymes (aminopeptidases and proteases) were found and they are belived to be the major barrier against the absorption of peptide drugs, such as calcitonin, insulin and desmopressin [33]. Thus, enzymes exist in the nasal mucosa may affect the pharmacokinetic and pharmacodynamic profile of nasally applied drugs.

In this context, although the nasal first-pass metabolism is usually weaker than hepatic and intestinal ones it cannot be ignored.

Mucociliary clearance

The function of mucociliary clearance system is to remove foreign substances and particles from the nasal cavity, consequently preventing them from reaching the lower airways. Nasally administered formulation can be cleared from the nasal cavity with a half-life of clearance of about 15 min with the result of limiting time available for absorption [34]. The normal mucociliary transit time in humans has been reported to be 12-15 min [35]. Rapid mucocliliary clearance of drug formulations that are deposited in the nasal cavity is thought to be an important factor underlying the low bioavailability of intranasally administered drugs. Some drugs, hormonal changes in the body, pathological conditions, and formulation factors especially rheology are reported to affect mucociliary clearance and in turn exert significant influence on drug permeability.

Physical condition of the nasal mucosa

The condition of the nasal mucosa can have an important effect on drug absorption. There are times when the mucosa is crushing, bleeding, or dry. One may be suffering from rhinorrhea, sinitis, or nasal infection. In people suffering from severe nasal allergies, an excessive nasal secretion can wash away the formulation before the drug has a chance of getting absorbed through the mucosa or before acting locally [36].

Ideal drug candidate for nasal delivery

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

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

Methods used to study nasal absorption in rats

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

In-situ method

Spague-Dawley male rats, weighing ~300 g each, are normally used. The rats are anaesthetized by i.p. injection of 50 mg/kg sodium pentobarbital. After an incision is made in the neck of the rats, the trachea is cannulated with a polyethylene tube. Another tube is inserted through esophagus to the posterior part of the nasal cavity. This tube served to introduce the perfusing solution into the nasal cavity. The nasopalatine is closed with an adhesive agent to prevent the drainage of the drug solution from the nasal cavity into the mouth. Various drug solutions with

volume ranging from 3-20 ml are placed in a water jacketed baker (20 ml) and keep at 37°C by means of a circulating water bath. Each solution is circulated through the nasal cavity of the rat by means of a polystaltic pump at a rate of 2-3 ml/min. The perfusion solution passes out from the nostrils through the funnel and into the beaker again. The solution is stir constantly using a manetic stirring bar (Fig. 2). The samples solution is withdrawn by a 100 µl syringe. The extent of absorption is determined over a period of 1 h by analyzing periodically the amount of drug remaining in the perfusing solution.

The most significant advantage of this is that one can screen several drugs easily and conveniently using standard analytical procedures. Furthermore, if the study is conducted using different perfusing volume, one can use the easily determined in-situ data to predict the in-vivo rate of absorption.

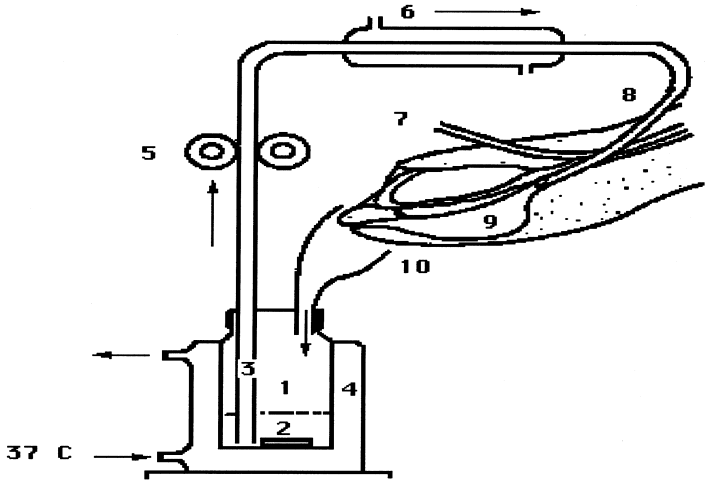

Fig. 2. Experimental set-up for the in situ nasal perfusion experiment. (1) Drug reservoir; (2) magnetic stirring bar; (3) tygon tube cannulation; (4) water jacketed beaker; (5) polystaltic pump; (6) water bath; (7) trachea cannulation; (8) esophagus; (9) nasal cavity; (10) funnel.

In-vivo in-situ method

In this method, small volumes of the drug 50-100 µl are administered to the nasal cavity. The concentration of the drug in the nasal cavity is determined utilizing simple analytical procedures. Furthermore, the data generated can be used directly to predict in-vivo absorption rates.

Fig. 3 shows the experimental arrangement for the in-vivo in-situ nasal experiments. The surgical procedure is similar to that described for the in-situ recirculation studies, except that a glass tube (3 cm long and 0.3 mm in diameter with one end sealed) is inserted into the posterior nasal cavity through the esophagus to keep the solution in the nasal cavity. Prior to administering the drug, the nasal cavity is carefully washed with 10 ml of Ringer's buffer to remove all traces of blood. One hundred-microlitre aliquots of solutions containing drug are placed in one nostril by means of micropipette. At an appropriate time interval, the nasal cavity is rinsed with 3.9 ml of ringer's buffer using peristaltic pump, and the experiment is terminated.

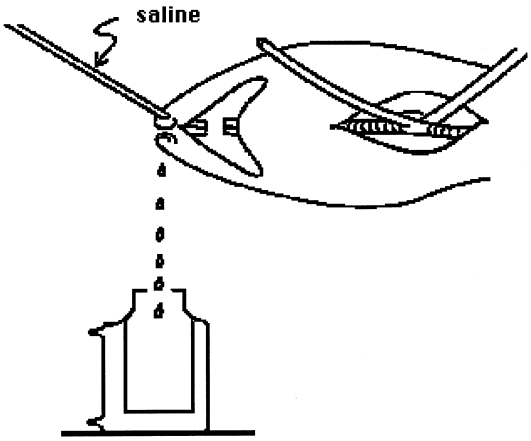

Fig. 3. Experiment set-up for the in-vivo in-situ nasal absorption experiment.

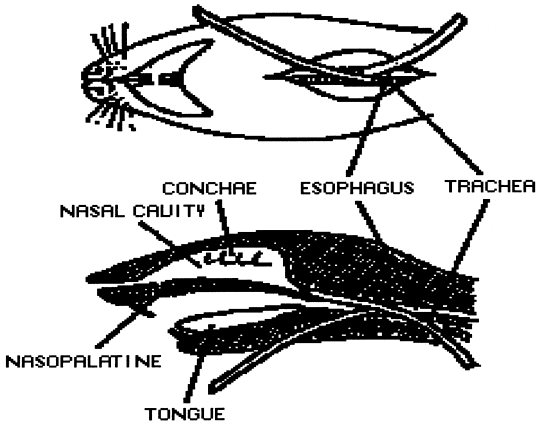

Fig. 4. Diagram of the surgical procedure of nasal absorption in the rat

Table 1: List of prescription nasal product currently on the market

No.	Product	Drug	Indication	Manufacturer
1	BeconaseÒ AQ Nasal Spray	Beclomethasone dipropionate monohydrate	Symptomatic treatment of seasonal and perennial allergic rhinitis	Allen and Hanbury's/Glaxo Wellcome Inc.
2	VancenaseÒ AQ Nasal Spray	Beclomethasone dipropionate monohydrate	Symptomatic treatment of seasonal or perennial allergic rhinitis	Schering Plough Corp.
3	RhinocortÒ Nasal Inhaler	Budesonide	Management of symptoms of seasonal and perennial allergic rhinitis and non-allergic perennial rhinitis	Astra USA, Inc.
4	Stadol NSÒ Nasal Spray	Butorphanol tartrate	Management of pain including migraine headache pain	Bristol Myers Squibb
5	MiacalcinÒ Nasal Spray	Calcitonin—salmon	Post-menopausal osteoporosis	Sandoz Pharmaceutical Corp.
6	NasalcromÒ Nasal Solution	Cromolyn sodium	Symptomatic prevention and treatment of seasonal or perennial	Fisons Corp. Prescription

			rhinitis	Products
7	DDAVPÒ Nasal Spray	Desmopressin acetate	Prevention and control of polydipsia, polyurea, and dehydration in patients with diabetes insipidus	Rhone Poulenc Rorer
8	StimateÒ Nasal Spray	Desmopressin acetate	Hemophilia A, von Willebrand's disease (type 1)	Rhone Poulenc Rorer
9	DecadronÒ Phosphate TurbinaireÒ	Dexamethasone	Treatment of inflammatory nasal conditions or nasal polyps	Merck and Co., Inc.
10	NasalideÒ Nasal Solution	Flunisolide	Symptomatic prevention and treatment of seasonal or perennial rhinitis	Roche Laboratories
11	FlonaseÒ Nasal Spray	Fluticasone propionate	Management of seasonal and perennial rhinitis	Allen and Hanbury's/Glaxo Wellcome Inc.
12	SynarelÒ Nasal Solution	Nafarelin acetate	Central precocious puberty; endometriosis	Roche Laboratories
13	SyntocinonÒ Nasal Spray	Oxytocin	Promote milk ejection in breast feeding mothers	Sandoz Pharmaceutical Corp.
14	NasacortÒ Nasal Inhaler	Triamcinolone acetonide	Treatment of seasonal and perennial allergic rhinitis	Rhone Poulenc Rorer

Sources: Physicians' Desk Reference for Nonprescription Drugs, 1994, 15th ed., published by Medical Data Production Company, Montvale, NJ, and Handbook of Nonprescription Drugs, 1993, 10th ed., published by The American Pharmaceutical Association, Washington, DC.

In-vivo method

In this method the drug is directly deposited into the nasal cavity and blood samples are periodically withdrawn and analyzed. In large animals such as dogs, sheep, and monkeys the drug is administered while the animal is under anesthesia and care should be taken to minimize the physical loss of the drug due to drainage.

The surgical procedure described by Huang et. al. [37] is performed on an anesthetized rat (Fig. 4). Since this method utilizes a closed and confined system, the data obtained is very reproducible and reliable. Furthermore, this model can also be used to predict the absorption profile of the drugs in other species as dogs and humans.

CONCLUSION

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

REFERENCES

[1] I. Illum, *J Pharm Sci*., **2007**, 96, 473–83.
[2] L. Illum, *J Pharm Pharmacol*., **2004,** 56, 3–17.

[3] W. H. Frey, *Drug Deliv Technol*., **2002**, 2, 46–9.
[4] T. K. Vyas, A. Shahiwala, S. Marathe, A. Misra, *Curr Drug Deliv*., **2005**, 2, 165–75.
[5] R. G. Thorne, G. J. Pronk, V. Padmanabhan, *Neuroscience*., **2004**, 127, 481–96.
[6] R. G. Thorne, G. Pronk, W. H. Frey, *Soc Neurosci Abstr*., **2000**, 26, 1365.
[7] J. P. Yang, H. J. Liub, S. M. Chenga, Z. L. Wanga, X. Chenga, H. X. Yuc, X. F. Liua, *Neurosci Lett*., **2009**, 449, 108–11.
[8] T. M. Ross, P. M. Martinez, J. C. Renner, R. G. Thorne, L. R. Hanson, W. H. Frey, *J Neuroimmunol*., **2004**, 151, 66–77.
[9] M. F¨oldi, *Lymphology*., **1996**, 29, 1–9.
[10] A. Yamamoto, T. Iseki, M. Ochi-Sugiyama, N. Okada, T. Fujita, S. Muranishi, *J Control Release*., **2001**, 76, 363–74.
[11] M. Hinchcliffe, L. Illum, *Adv Drug Deliv Rev*., **1999**, 35, 199–234.
[12] C. R. Behl, H. K. Pimplaskar, A. P. Sileno, J. Demeireles, V. D. Remo, *Adv Drug Deliv Rev*., **1998**, 29, 89–116.
[13] D. C. Corbo, J. C. Liu, Y. W. Chien, *J Pharm Sci*., **1990**, 79, 202–206.
[14] A. Ninomiya, K. Ogasawara, K. Kajino, A. Takada, H. Kida, *Vaccine*., **2002**, 20, 3123–29.
[15] C. Yang, H. Gao, A. Mitra, *J Pharm Sci*., **2000**, 90, 617–24.
[16] A. M. Al-Ghananeem, A. A. Traboulsi, L. W. Dittert, A. A. Hussain, *AAPS Pharm Sci Tech*., **2002**, 3, 1–8.
[17] A. Heidari, H. Sadrai, J. Varshosaz, *Drug Deliv*., **2006**, 13, 31-8.
[18] I. A. Alsarra, A. Y. Hamed, G. M. Mahrous, G. M. El Maghraby, A. A. Al-Robayan, F. K. Alanazi, *Drug Dev Ind Pharm*., **2009**, 35, 352-62.
[19] N. Kilian, D. G. Müller, *Int J Pharm*., **1998,** 163, 211-17.
[20] N. M. Zaki, G. A. Awad, N. D. Mortada, S. S. Abd ElHady, *Int J Pharm*., **2006**, 327, 89-96.
[21] C. Huang, R. Kimura, R. Nassar, A.A. Hussain, *J. Pharm. Sci*., **1985**, 74, 1298–301.
[22] I. Gonda, E. Gipps, *Pharm. Res*., **1990**, 7, 69–75.
[23] A. Harris, M. Ohlin, E. Svensson, S. Lethagen, I. Nilsson, *J. Pharm. Sci*., 1989, 78, 470–71.
[24] L. Malm, *Acta Otolaryngol. (Stockh.)*., **1974**, 78, 90–7.
[25] H.B. Richerson, P.M. Seeboham, *J. Allergy*., **1968**, 41, 269–84.
[26] M. Bende, *Acta. Otol*., **1983**, 96, 523–27.
[27] P. Olson, M. Bende, *Ann. Otol. Rhinol. Laryngol*., **1985**, 94, 153–57.
[28] B. Paulsson, M. Bende, P. Ohlin, *Acta Otolaryngol. (Stockh.)*., **1985**, 99, 140–4.
[29] K. Anderson, M. Bende, *Ann. Otol. Rhinol. Laryngol*., **1984**, 93, 179–82.
[30] M. Bende, K. Flysberg, I. Larsson, P. Ohlin, P. Olson, *Acta Otolaryngol. (Stockh.)*., **1983**, 96, 277–80.
[31] M. Lung, J. Wang, *Ann. Otol. Rhinol. Laryngol*., **1985**, 94, 198–201.
[32] S. Dimova, M. E. Brewster, M. Noppe, M. Jorissen, P. Augustijns, *Toxicol In Vitro*., **2005**, 19, 107-22.
[33] V. H. Lee, A. Yamamoto, *Adv Drug Deliv Rev*., **1990**, 4, 171-207.
[34] R. J. Soane, M. Frier, A. C. Perkins, N. S. Jones, S. S. Davis, L. Illum, *Int J Pharm*., 1999, 178, 55–65.
[35] F.W. Merkus, J. C. Verhoef, N. G. Schipper, E. Marttin, *Adv Drug Deliv Rev*., **1998**, 29, 13–38.
[36] E.L. Smith, R.L. Hill, A. Borman, *Biochem. Biophys. Acta*., **1958**, 29, 207–14.
[37] E.G. Brittebo, J.J. Rafter, *Steroid. Biochem*., **1984**, 20, 1147.