CHAPTER 6

ALTERNATIVE APPLICATIONS FOR DRUG DELIVERY: NASAL AND PULMONARY ROUTES

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Abstract: For treatment of human diseases, nasal and pulmonary routes of drug delivery are gaining increasing importance. These routes provide promising alternatives to parenteral drug delivery particularly for peptide and protein therapeutics. For this purpose, several drug delivery systems have been formulated and are being investigated for nasal and pulmonary delivery. These include liposomes, proliposomes, microspheres, gels, prodrugs, cyclodextrins and others. In this chapter, nasal and pulmonary drug delivery mechanisms and some of the relevant drug delivery formulations are evaluated

Keywords: drug delivery systems, pulmonary drug delivery, nasal drug delivery, peptide delivery, protein delivery, liposomes, microspheres

1. INTRODUCTION

Only few decades ago, pulmonary and nasal (intranasal) applications of drugs were not as widespread as it is today. In the year 2000, there were 27 products on the U.S. market for intranasal use, with more than half of these having obtained FDA approval between the years 1990 and 2000. With ever-increasing pharmaceutical technology and numerous medicinal opportunities for intranasal administration, its popularity will most likely continue [1].

Pulmonary and intranasal drugs may be administered for local treartment or systemic action based on the therapeutic intention. Physicotropic drugs, hallucinogenes (cocain), snuffs, antibiotics, vasoconstrictors, antihystaminics and local anesthetics are the examples of nasal drugs administered locally in several dosage forms like nasal solutions, ointments and sprays. Recent observations of side effects of intranasally administered antihistaminic and vasoconstrictor drugs have leaded to their systemic use [2]. Intranasal drugs for systemic action include treatments for migraine headaches, calcium supplementation, Vitamin B12 deficiency and pain

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relief as well as other therapeutic indications. In addition to either local or systemic effects, drugs may be intended for acute or chronic treatments [1].

Additionally, delivery of drugs to or via the respiratory tract can offer several advantages over alternative routes of administration. In general, pulmonary administration of drugs is more satisfactory if the intention is to achieve local action within the respiratory tract.

2. ADVANTAGES OF INTRANASAL DRUG ADMINISTRATION

With optimized formulations, intranasal administration presents many benefits when compared to alternative delivery routes (1–3). These include:

- Not only is the nasal cavity easily accessible, it is virtually non-invasive;
- In most cases, intranasal administration is well tolerated;
- Only slight irritation may occur due to the chemical nature of substance delivered;
- Hepatic first-pass metabolism is avoided with intranasal delivery;
- Destruction of drugs by gastric fluid is not a concern;
- Intranasal mucosae has a big number of microvilli, therefore has a high surface area (150 cm^2);
- Subepithelial tissue has a high vascularization;
- It offers lower doses with more rapid attainment of therapeutic blood levels;
- Quicker onset of pharmacological activity;
- Fewer side effects;
- High total blood flow per cm^3;
- Porous endotheliel basement membrane;
- Drug is delivered directly to the brain along the alfactory nerves.

3. WHICH TYPES OF DRUGS ARE ADMINISTERED INTRANASALLY?

Since many years, nasal route has been used for delivery of drugs and similar other bioactive substances such as illicit drugs, psycotrops, snuffs, etc. Generally the following material are being considered for intranasal delivery:

- Drugs hardly absorbed by oral route;
- Drugs metabolized in the GI tract; and
- Drugs exposed to the first-pass effect of liver can be administered intranasally [2, 3].

4. NASAL ANATOMY AND PHYSIOLOGY

Nasal cavity is circulated by cranium base at the bottom, hard palate at the top and nares and pharynx. The distance from the tip of the nose to the pharyngeal wall is about 10–14 cm and has a 160 cm^2 surface area. The nasal septum divides the nose into two nasal cavities, each with a 2–4 mm wide slit opening and contains three distinct functional regions: vestibular, respiratory and olfactory [1, 2, 4].

The respiratory region contains the largest surface area and is located between the vestibular and olfactory regions. The respiratory region is the most important part for drug delivery administered systemically. The vestibular region is located closest to the nasal passage opening, contains long hairs and serves as a filter for incoming particles. The olfactory region is located in the uppermost portion of each cavity and opposite the septum. This region is responsible for smelling [1].

Nasal mucosa has exopeptidases (like aminopeptidase, diaminopeptidase etc.) and endopeptidases (like cerynproteinase, cysteinproteinase, metalloproteinase, etc.). These enzymes cause enzymatic degredation of peptides and proteins during absorption [5].

The primary function of the nose is olfaction – it heats and humidifies inspired air and also filters airborne particles [6]. Consequently, the nose functions as a protective system against foreign material [7]. The vestibular area serves as a buffer system; it functions as a filter of airborne particles [8]. The olfactory epithelium is capable of metabolising drugs [6]. The respiratory mucosa is the region where drug absorption is optimal [2].

5. NASAL ABSORPTION MECHANISMS

Intranasally administered drugs aimed to obtain systemic effect, pass to the circulation via nasal barrier (epithelium).

The epithelium of the respiratory region consists of four different cell types: basal, mucus-containing goblet, ciliated columnar, and nonciliated columnar. The ciliated columnar cell is the most predominant. The cilia beat in a wave-like, coordinated manner to transport mucus and trapped particles to the pharynx area for subsequent ingestion. Cells in the respiratory region are covered by approximately 300 microvilli, which greatly increase the surface area of the nasal cavity. The respiratory region also contains the inferior, middle and superior turbinates. The lamina propria, below the epithelium houses blood vessels, nerves and both serous and mucus secretory glands [1].

A drug may cross the nasal mucosa by three different mechanisms [1,9]:

i. Transfer via transcellular or simple diffusion across the membrane;
ii. Paracellular transport: Movement through the spaces between cells and tight junctions; and:
iii. Transcytosis (particle internalization by vesicles).

5.1 MUCUS

Mast cells contain polymorphonuclear leucocytes and eosynophyls. Mucus consists of salt 2.5–3%, musin 1–2% (sulphurated scyderoprotein) and water 95%. Lysozymes, enzymes and immunoglobulins, in addition to other proteins, may all be found in the mucus. Proteins and carbohydrates are secreted from endoplasmic reticulum and golgi substance, respectively [2]. Mucus is produced about 1–2 l everyday [2,10]. The mucus consists of an outer viscous layer of mucus and watery

layer located along the mucosal surface [1, 10]. The pH of secretions ranges from 5.5 to 6.5 and from 5.0 to 6.7 in adults and children, respectively [1, 11]. The epithelium is covered with new mucus layer approximately every 10 min [10].

Nasal mucosa is covered by cilia, which does not have the same temperature and movement at every point. The optimum temperature is 18–37°C for mucociliar movement and is blocked at 7–12°C [2].

Nose shows a barrier effect for the inspirated particles and viruses reaching it externally. These particles are retained by the mucus covering the epithelium. The viscous layer of mucus, along with entrapped particles, is transported to the nasopharyngeal area for ingestion [2, 12]. The cilia beat at a frequency which is approximately 10–13 Hz [1, 13].

Mucociliar clerance is affected by several factors such as viscoelasticity of mucus, the thickness of mucus layer, gravity and air flux [2].

6. FACTORS AFFECTING NASAL DRUG ABSORPTION

The physicochemical properties of the drug, nasal mucociliary clearance and nasal absorption enhancers are the main factors that affect drug absorption through the nasal mucosa. One of the greatest limitations of nasal drug delivery is inadequate nasal absorption. Several promising drug candidates cannot be exploited via the nasal route because they are not absorbed well enough to produce therapeutic effects. This has led scientists to search for ways to improve drug absorption through the nasal route [3, 14]. The following parameters need to be considered in order to optimize nasal drug delivery.

a) *Physicochemical Properties of the Drug*: The rate and extent of drug absorption may depend upon many physicochemical factors including the aqueaus-to-lipid partititon coefficient of the drug, the pKa, the molecular weight of the drug, perfusion rate and perfusate volume, solution pH and drug concentration [15]. It has been concluded that in vivo nasal absorption of compounds of molecular weight of less than 300, is not significantly influenced by the physicochemical properties of the drug [16]. There is a direct correlation between the proportion of the nasally absorbed dose and the molecular weight [17].

b) *Mucociliary Clearance*: Particles entapped in the mucus layer are transported with it and, thereby, effectively cleared from the nasal cavity. The combined action of mucus layer and cilia is called “mucociliary clearance”. This is an important, non-specific, physiological defence mechanism of the respiratory tract to protect the body against noxious inhaled materials [3, 12]. The normal mucociliary transit time in humans has been reported to be 12 to 15 min [18]. The factors that affect mucociliary clearance include physiological factors such as age, sex, posture, sleep, exercise [19, 20]; common environmental pollutants such as sulphur dioxide, sulphuric acid, nitrogen dioxide, ozone, hair spray and tobacco smoke [21]; diseases including asthma, bronchiectasis, chronic bronchitis, cystic fibrosis, acute respiratory tract infection, immotile cilia syndrome, primary ciliary dyskinesia [21]; drugs [22]; and additives [23].

c) *Nasal Absorption Enhancers:* In order to solve the insufficient absorption of drugs, absorption enhancers are employed. The absorption enhancement mechanisms can be grouped into two classes [3]:
   i. Physicochemical Effects: Some enhancers can alter the physicochemical properties of a drug in the formulation. This can happen by alterning the drug solubility, drug partition coefficient or by weak ionic interactions with the drug; and
   ii. Membrane Effects: Many enhancers show their effects by affecting the nasal mucosa surface [24].

Surfactants, bioadhesive polymer materials, drug delivery systems, cyclodextrins, bile salts, phosphatidylcholines and fusidic acid derivatives are known as absorption enhancers [2, 3].

Nasal absorption of peptides and proteins through nasal mucosa is limited by their high molecular weight. Nasal bioavailability of peptides and proteins is affected by mucociliar clearance and enzyme activity in the nasal cavity. Therefore, nasal bioavailability enhancement can be achieved by different approaches such as modification of chemical structure, prodrug use, addition of absorption enhancers/enzymes and use of mucoadhesive dosage form [5].

7. DRUG DELIVERY SYSTEMS ADMINISTERED INTRANASALLY

For the enhancement of nasal bioavailability, a drug delivery system should have the following properties [2]:

- It should adhere to the nasal mucosa;
- It should pass through the mucus;
- It should cause the formation of viscous layer;
- It should have low clearance;
- It should keep the stability of the drug; and
- It should release the drug slowly.

Some of the commonly used drug delivery systems for nasal administration are explained in the following sections.

7.1. Liposomes and Proliposomes

Liposomes have been used extensively for bioactive delivery by several routes. Alpar et al [25, 26] studied the potential adjuvant effect of liposomes on tetanus toxoid, when delivered via the nasal, oral and I.M. routes compared to delivery in simple solution in relation to the development of a non-parenteral immunization procedure, which stimulates a strong systemic immunity. They found that tetanus toxoid entrapped in DSPC liposomes is stable and is taken up intact in the gut [25, 26].

Intranasal administration of calcitonin-containing charged liposomes in rabbits was investigated to evaluate the in vivo calcitonin absorption performance. Significant level of accumulation of positively charged liposomes on the negatively charged nasal mucosa surface was reported [27]. Plasma calcitonin concentration and pharmacokinetic parameters were calculated. Intranasal bioavailability demonstrated an order of calcitonin containing positively charged liposomes > calcitonin containing negatively charged liposomes > calcitonin solution. The significant enhancement of intranasal bioavailability of calcitonin for positively charged liposomes may be due to charge interaction of positively charged liposomes with the negatively charged mucosa. Marked accumulation of positively charged liposomes on the negatively charged nasal mucosa surface caused high retention of positively charged liposomes on the nasal mucosa which resulted in an increase in residence time with high local concentration of calcitonin [27].

The major cause of mortality in patients with cystic fibrosis (CF) is a lung malfunction. A DNA–liposome formulation was delivered to the nasal mucosa of CF patients in repeated doses. It was reported that the DNA containing liposomes can be succesfully re-administered without apparent loss of efficacy for CF treatment [28].

In a comparative permeability study, insulin liposomes have permeated more effectively after pre-treatment by sodium glycocholate when compared to non-encapsulated insulin solution [29].

Goncharova et al [30] have mentioned the importance of nasal mucosa for the immunisation against Tick-Borne encephalitis. To study intranasal immunization against TBE virus, biodegredable micelles, cationic liposomes and live attenuated bacterial/viral vectors were chosen. The results showed the expression of the gene in transfected cells, thereby demonstrating that the liposomal formulations are suitable for mucosal immunization [30].

In another study using nicotine proliposomes, it has been reported that nicotine delivery was prolonged in rats when administered intranasally [31].

7.2. Microspheres

Microspheres of different ingredients have been evaluated as nasal drug delivery systems. Microspheres of starch, albumin, chitosan, and DEAE-dextran have been investigated. Chemical class of the polymer, binding ability, penetration, polymer concentration, pH, and hydration level are among the factors affecting intranasal delivery [1].

Degredable Starch Microspheres (DSM) is the most frequently used microsphere system for nasal drug delivery and has been shown to improve the absorption of insulin in particular and other bioactive compounds in general. Insulin administered in DSM to rats resulted in a rapid dose-dependent decrease in blood glucose [32,33]. In another study in rabbits, apomorphine release from DSM microspheres was compared with CMC and lactose applied intranasally and the fastest absorption was obtained with lactose [34].

Illum et al [35] introduced well-characterized bioadhesive microspheres for prolonging the residence time in the nasal cavity of human volunteers. The slowest clearance was detected for DEAE-dextran, where 60% of the delivered dose was still present at the deposition site after 3h. On the contrary, these microspheres were not successful in promoting insulin absorption in rats [36].

Human growth hormone (hGH)-loaded microparticles prepared by polycarbophil-cysteine (PCP-Cys) in combination with glutathione (GSH) represented a promising tool for the delivery of hGH for nasal bioavalability [37].

In another study, microspheres intended as a sustained release carrier for oral or nasal administration were prepared by polyacrylic acid molecules [38]. A model drug oxyprenolol HCl was chosen and it was found that some of the formulation variables can influence the release characteristics. The internal structure (by X-ray diffraction, thermal analysis and optical microscopy) and release mechanism were investigated. The work revealed the potential of this pharmaceutical system as an alternative controlled-release dosage form for the intranasal administration [38].

7.3. Gels

Chitosan and chitin have been suggested for use as vehicles for the sustained release of drugs. A sustained drug release based on chitosan salts for vancomycin hydrochloride delivery has been investigated by using different chitosan salts like aspartate, chitosan glutamate and chitosan hydrochloride. Vancomycin hydrochloride was used as the peptidic drug, the nasal sustained release of which should avoid first-pass metabolism in the liver. This in vitro study evaluated the influence of chitosan salts on the release behaviour of vancomycin hydrochloride and it has been reported that in vitro release of vancomycin was retarded mostly by chitosan hydrochloride [39]. Similar results were obtained by Tengamuay et al [40].

Vila et al [41] have prepared chitosan nanoparticles by an ionics cross-linking technique and used tetanus oxoid as model antigen. These nanoparticles were administered intranasally to mice in order to study their feasibility as vaccine carriers. In vitro release studies showed an initial burst followed by an extended release of active toxoid. Following intranasal administration, tetatanus toxoid-loaded chitosan nanoparticles elicited an increasing and long-lasting immunogenity as compared to the fluid vaccine. Interestingly, the ability of these nanoparticles to provide improved access to the associated antigen to the immune system was not significantly affected by the chitosan molecular weight. High and long lasting responses could be obtained with low molecular weight chitosan molecules.

Additionally, the response has not been influenced by the chitosan dose. This group concluded that nanoparticles made of low molecular weight chitosan are promising carriers for nasal vaccine delivery [41].

It was observed that the chitosan delivery (microspheres) of a drug had significantly reduced rates of clearance from the nasal cavity as compared to the control

(solution). Chitosan delivery systems have the ability to increase the residance time of drug in the nasal cavity thereby providing the potential for improved systemic medication [42].

Insulin loaded chitosan nanoparticles have been prepared with trehalose as cryoprotectant by freeze-drying method. The in vivo evaluation of chitosan nanoparticles in rabbits revealed that these nanoparticles are able to reduce glucose levels to a greater extent than insulin-chitosan solution when applied intranasally [43,44].

Nasal absorption of nifedipine from gel preparations, PEG 400, aqueous carbopol gel and carbopol-PEG has been studied in rats. Nasal administration of nifedipine in PEG resulted in rapid absorption and high c_{max}; however, the elimination of nifedipine from plasma was very rapid. The plasma concentration of nifedipine in aqueous carbopol gel formulation was very low when administered intranasally. The use of PEG 400 in high concentrations in humans should be considered carefully. This is because PEG 400 is known to cause nasal irritation in concentrations higer than 10% [45].

Nasal absorption of Calcitonin and Insulin from polyacrilic acid gel has been investigated in rats. It has been reported that nasal absorption of insulin is greater from 0.15% (w/v) polyacrylic acid gel than from 1% (w/v) gel. There seem to be an optimum concentratiton and possibly an optimum viscosity for the polyacrilic acid gel base [46].

Ugwoke et al [47] have prepared apomorphine mucoadhesive preparations incorporating Tc-99m labelled colloidal albumin. Drug residence time in rabbit nasal cavity was evaluated by gamma scintigraphy using different agents like Carbopol 971P, CMC and lactose (control), each with or without apomorphine. The use of mucoadhesives such as Carbopol 971P or CMC in nasal gels increases their residence time within the nasal cavity and provides opportunity for sustained nasal drug delivery [47].

7.4. Other Delivery Systems

Phosphatidylcholines are surface-active amphiphilic compounds present in biological membranes and liposomes. Several reports have appeared in the literature showing that these phospholipids can be used for enhancing the systemic nasal drug delivery [48].

Another intensive study has been put on fusidic acid derivatives and among these Sodium Tauro-24, 25-dihydrofusidic acid (STDHF) is the most extensively studied derivative of fusidic acid. STDHF was reported as a good candidate for the transnasal delivery of drugs like insulin, octreotide, and human growth hormone [49–52].

Radioimmunoactive bioavailability of intranasal salmon calcitonin was determined in healthy human volunteers. The nasal absorption of calcitonin was improved by STDHF and it caused a limited transient irritation of the nasal mucosa in some subjects [53].

Didecanoyl-L-phosphatidylcholine (DDPC) has been used as enhancer for intranasal insulin administration in human volunteers. It was observed that intranasal insulin administration was absorbed in a dose dependent manner with slight or no nasal irritation [54]. Another study revealed that Glycyrrhetinic acid derivatives enhance insulin uptake without nasal irritaition or insulin degredation [55].

8. CYCLODEXTRINS

Several compounds have been investigated for their nasal absorption enhancement. Cyclodextrins are observed as the best-studied group of enhancers. The most-studied of them are: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, methylcyclodextrin and hydroxypropyl β-cyclodextrin. Among these, β-cyclodextrin is being considered for possessing a GRAS (Generally Recognised As Safe) status [56, 57].

Cyclodextrins have been used successfully to increase the absorption of many substances including salmon calcitonin [58, 59], insulin [60] and human growth hormone [61].

9. PRODRUGS

The utility of nasal route for the systemic delivery of 17-beta-estradiol was studied using water-soluble prodrugs of 17-beta-estradiol. This method was examined to determine if it would result in preferential way to the brain. In vivo nasal experiments were carried out on rats. Absorption was fast following nasal delivery of prodrugs with high bioavailability. These products were found to be capable of producing high levels of estradiol in the cerebral spinal fluid and as a result may have a significant value in the treatment of Alzheimer's disease [62].

10. PULMONARY DELIVERY SYSTEMS

Studies on the delivery of drugs to or via the respiratory tract have been carried out in the recent 25 years. This route can offer considerable advantages over other drug dministration ways as listed below [63, 64]:

- Provides local action within the respiratory tract;
- Provides rapid drug action;
- Provides reduced dose;
- Allows for a reduction in systemic side-effects;
- Reduces extracellular enzyme levels compared to GI tract due to the large alveolar surface area;
- Reduces evasion of first pass hepatic metabolism by absorbed drug; and
- Offers the potential for pulmonary administration of systemically active materials.

On the other hand, it has some disadvantages as well [63, 64], which include:

- The duration of activity is often short-lived due to the rapid removal of drug from the lungs or due to drug metabolism; and
- Necessitates frequent dosing.

10.1. Which Types of Drugs are Administered via Pulmonary Route?

Drugs are absorbed from the lungs mainly by the following two mechanims:
i) Passive diffusion; and
ii) Active endocytosis [65].
Drugs for asthma, allergy and chronic obstructive pulmonary diseases are used via pulmonary route. Beta agonists, anticholinergic drugs, mucolytics and corticosteroids are some examples for these drugs [5].

10.2. Pulmonary Anatomy and Physiology

From the trachea, the airways divide dichotomously to form bronchi, respiratory and terminal bronchioles and ultimately alveoli. The role of the airways gradually changes from one of conduction by the large airways to one of gaseous exchange for the peripheral lung (respiratory bronchioles and alveoli) [64].

Nearly 95% of the alveolar cells are Type I cells which are 5 μm in size. Type II cells are 10–15 μm in size and secrete surfactants which are important for the function of the lungs. Phosphatidylcholine and phosphatidylglycerol are the main phospholipids of lung surfactants [65]. Lung surfactants deposit a monomolecular film on the alveoli and prevent pulmonary oedema and provide protection against infections [66].

10.3. Factors Affecting Pulmonary Delivery

The size of inhaled particles is the main factor affecting pulmonary delivery. The important size property for deposition in the lungs is called aerodynamic diameter. It is determined by the actual size of the particle, its shape and its density. The particles in the aerodynamic size range of about 3.5–6.0μm can penetrate, to some extent, at slow inspiratory flow rates beyond the central airways into the peripheral region of the lungs. On the other hand, particles less than 3.5μm and greater than about 0.5μm will mostly bypass the bronchial airways during inhalation and penetrate almost entirely to the deep lung. Larger particles are dominated by their inertial mass and will impact in upper airways due to their inertia. Smaller particles (with aerodynamic diameters less than 0.5μm) are dominated by thermal interactions with the air molecules and will diffuse to the respiratory tract surfaces during inhalation [67].

Diseases of the respiratory tract and hygroscopicity of the powders are the other factors affecting pulmonary delivery [67].

10.4. Pulmonary Drug Delivery Systems

There are three types of conventional methods of inhalation delivery for the treatment of respiratory diseases [67]:

i. Pressurized Metered-Dose Inhalers (MDIs or pMDIs);
ii. Dry Powder Inhalers (DPIs); and
iii. Nebulizers.

The conventional inhalation systems are designed primarily to generate particles of suitable size for topical delivery to the airways.

The lung presents a very attractive route for the invasive delivery of systemically active compounds.

Among the modified-release carrier systems, liposomes are the most frequently used ones. The main advantage of the use of liposomes as drug carriers in the lung is that they can be prepared from phospholipid molecules endogenous to the lung as components of lung surfactant [68]. Secondly, liposomes help to develop controlled release systems for local and systemic delivery. Thirdly, improved pulmonary therapy and lower side-effects can be obtained by liposomal drugs.

Anticancer drugs (ARA-C, 5-fluorouracil), antimicrobials (pentamidin, amikasin, enviroksim), peptides (insulin, calcitonin), enzymes (superoxide dismutase), antiallergic and antihistaminic compounds (salbutamol, metaproterenol), immunosupressive (siklosporin) and antiviral (ribavirin) drugs are some examples of the active compounds used in the pulmonary delivery research (e.g. see Ref. 5). Atropine, benzylpenicillin, carboxyfluorescein, cytarabine, enviroxime, glutathione, glyceryltrinitrite, orciprenaline, oxytocine and pentamidine are other examples of several drugs delivered to the lungs of the animals [64].

Another group of researchers have been studying the delivery of the genetic drugs via the lungs [69, 70] while progress and improvements in the field are ongoing.

11. CONCLUSION

Nasal and pulmonary routes of drug delivery are increasingly gaining importance in drug therapy. Particularly, these routes are considered as alternative ways to parenteral route for peptide and protein therapeutics. It has been shown that intranasal and intratracheal administration to the mucosae are important routes and were found effective for the immunospecific reaction response. It has been reported that various therapeutic and vaccine formulations can be administered successfully by thes nasal and pulmonary routes. However, because of the many hurdles in administration, pulmonary delivery is not usually preferred as yet. In conclusion, nasal and pulmonary drug delivery systems, described in this chapter, seem particularly appropriate techniques for drug delivery with great futuristic potential applications.

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