Nasal drug delivery

CHAPTER CONTENTS

- Introduction
- Anatomy and physiology
- Drug delivery
  - Local delivery
  - Systemic delivery
  - Nasal vaccines
  - CNS delivery
- Nasal delivery systems
- Summery

Introduction

- Nasal delivery is used to provide a convenient and accessible route or rapidly and efficiently managing the localized symptoms associated with allergic rhinitis, nasal congestion and nasal infection.
- Drugs applied topically or such purposes include antihistamines, corticosteroids, sodium cromoglicate, sympathomimetics and antiseptics/ antibiotics (Table 38.1). These drugs are administered either in liquid form (from a spray or as drops) or as creams/ointments.

Table 38.1 Examples of medicines administered into the nasal cavity

Drug	Drug class	Use	Delivery system
Locally-acting preparations			
Azelastine hydrochloride	Antihistamine	Allergic rhinitis	Metered spray
Fluticasone propionate, beclometasone dipropionate, betamethasone sodium phosphate and budesonide	Corticosteroid	Allergic/perennial rhinitis	Nasal drops/Metered spray
Ephedrine hydrochloride and xylometazoline hydrochloride	Sympathomimetic	Nasal congestion	Nasal drops
Sodium cromoglicate	Cromoglicate	Allergic rhinitis	Metered spray
Ipratropium bromide	Antimuscarinic	Rhinorrhea	Metered spray
Chlorhexidine and neomycin	Antibacterial	Staphylococci elimination	Cream
Mupirocin	Antibacterial	MRSA elimination	Ointment
Preparations administered for systemic effects			
Desmopressin acetate	Pituitary hormone	Diabetes insipidus/ mild haemophilia	Metered spray
Fentanyl citrate	Opioid analgesic	Moderate/severe Pain	Metered spray
Nicotine	Alkaloid	Smoking cessation	Metered spray
Salmon calcitonin	Polypeptide hormone (calcium regulator)	Postmenopausal osteoporosis	Metered spray
Buserelin	Gonadorelin analogue	Prostate cancer/ endometriosis	Metered spray
Sumatriptan	$5HT_1$ agonist	Migraine	Unit-dose spray
Nasal Vaccines			
Influenza	Live attenuated virus	Vaccination	Pre-filled unit-dose syringe

Introduction-*continued*

- The intranasal route has also been exploited or the delivery of drugs to the systemic circulation (Table 38.1). There are several possible reasons for considering nasal route rather than the oral route. These include:

➢ the potential to elicit a rapid onset of action (e.g. in the treatment of pain, migraine and erectile dysfunction).

➢ the avoidance of gastrointestinal and hepatic pre-systemic metabolism (e.g. peptides(calcitonin) and drugs (e.g. hyoscine and morphine).,

➢ Patient compliance, ease of access, noninvasivness, lack of pain

Introduction-*continued*

- The lower cost in production in comparison with parenteral products (no requirement for the sterilization of the final product).
- The management of chronic disorders; providing the medicine does not induce irritation then it can be used or prolonged periods (perhaps alternating the use of nostrils).

The nasal cavity has also been utilized for the delivery of vaccines, particularly or infections associated with the respiratory tract such as influenza and possibly for tuberculosis. intranasal vaccination has been studied with a view to combating noroviruses, the measles and herpes viruses, diphtheria and tetanus microorganisms. An intranasal vaccine containing live attenuated influenza vaccine has been marketed (Table 38.1).

Introduction-*continued*

- Research has been aimed at the possibility of delivery of drugs directly to the CNS through the olfactory region in the upper reaches of the nasal cavity (avoiding the blood brain barrier). For treating conditions such as: Alzheimer's disease, brain tumours, epilepsy, pain and sleep disorders.

Anatomy and physiology

- The nasal cavity is 120–140 mm from the nostrils to the nasopharynx (Fig. 38.1) and is divided in two by the nasal septum.
- The total surface area of both cavities is about 160 cm2 and the total volume is about 15 mL. The first part of the nasal cavity (termed the nasal vestibule) contains the narrowest part of the nasal cavity with a cross-sectional area of 30 mm2 on each side.
- The lining of the vestibule changes from skin at the entrance, to a stratified squamous epithelium which extends over the anterior third of the entire nasal cavity.
- The nasal vestibule contains vibrissae (hairs) which filter out inhaled particles with an aerodynamic particle size greater than approximately 10 µm. Progression through the nasal cavity leads to the turbinate region. The turbinates are convoluted projections from the nasal septum which are lined with a pseudostratified columnar epithelium (80–90% of the total surface area of the nasal epithelium in man) composed of mucus-secreting goblet cells, ciliated and nonciliated cells and basal cells (Fig. 38.1).
- The apical surfaces of the ciliated and non-ciliated cells are covered with non-motile microvilli, which serve to increase the surface area of the epithelial cells. There are also approximately 100 motile cilia on each ciliated cell which are responsible for mucus transport.

Anatomy and physiology

- Serous and seromucous glands also contribute to nasal secretions.
- As air moves through the turbinate region via the meatuses (Fig. 38.1), the low rate of air flow in combination with the turbulence created by the shape of the turbinates encourages the air to make contact with the highly vascularized walls, enabling it to be warmed and humidifed.
- Particulates (5–10 µm) within the airstream, such as dust, pollen, microorganisms and pollutants have the potential to deposit on the viscoelastic mucous gel lining the turbinate walls. The cilia, beating within the periciliary fluid, engage with the underside of the mucus and propel the gel and the deposited particles to the nasopharynx, where they are either swallowed or expectorated.
- This process is termed mucociliary clearance and is able to clear mucus at a rate of about 7 mm min−1. About 20% of the inspired air is directed to the top of the turbinates where the olfactory region is located (Fig. 38.1). This is an area approximately 12.5 cm2 (~ 8% o the total surface area of the nasal epithelium in man) of nonciliated pseudostratified columnar epithelium traversed by 6–10 million olfactory sensory neurons which pass from the nasal cavity, between the epithelial (sustentacular) cells and through the cribriform plate to the olfactory bulb of the brain.

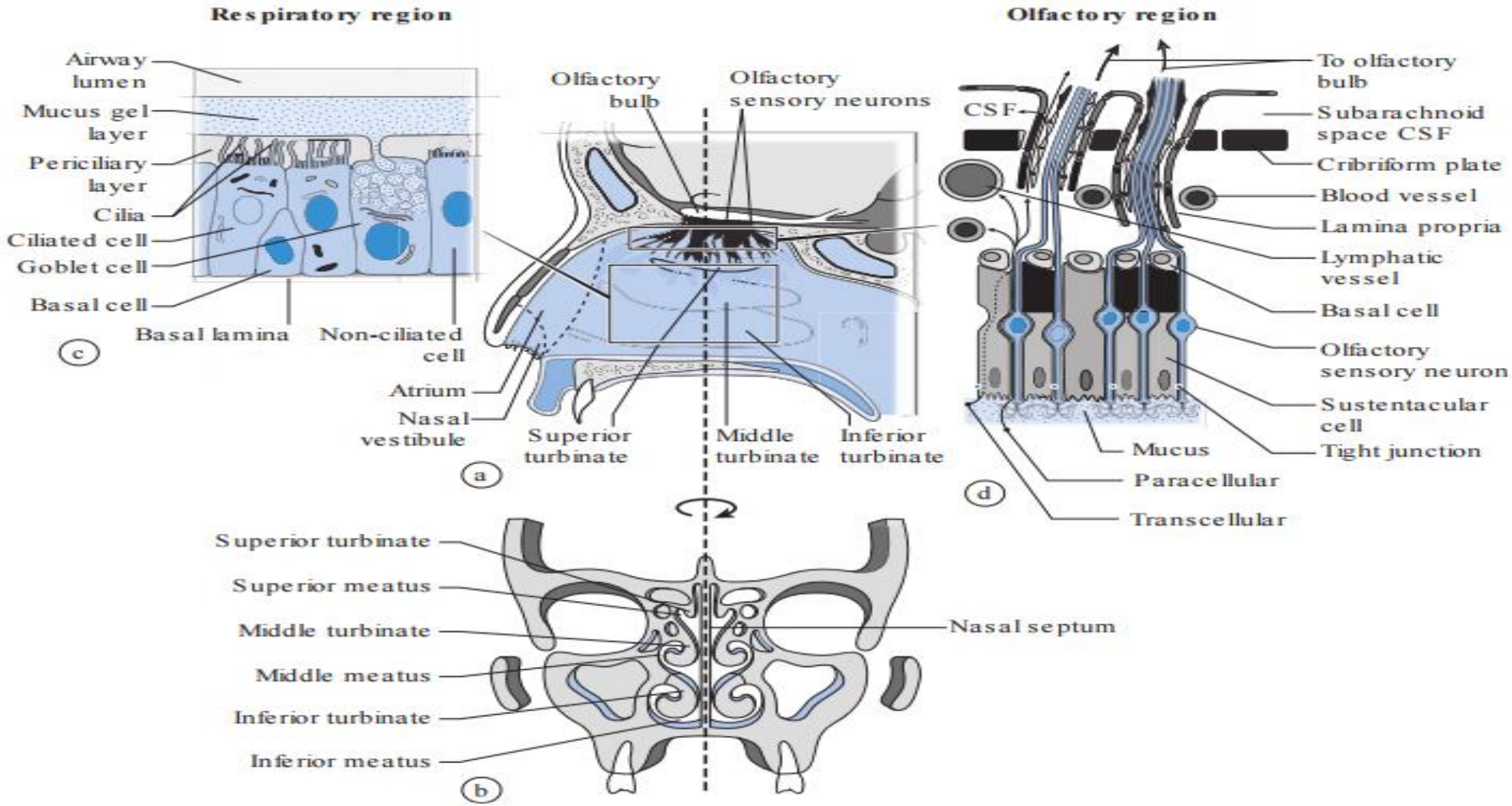


Figure 38.1 • Lateral wall of the nasal cavity **(a)** and cross-section through the middle of the nasal cavity **(b)**. The respiratory epithelium **(c)** and the olfactory epithelium **(d)**.

Drug delivery

- Certain constraints are imposed upon formulating preparations or the nasal route and two case studies, one a locally-acting drug (budesonide) and a second systemically-acting peptide drug (calcitonin) are given in Table 38.2.
- Nasal products formulation depends on:

- The solubility of the drug to be administered is a key determinant in the final formulation.
- The restricted volume that can be applied to the nasal cavity also impacts upon the nature of the resultant formulation.
- Generally, the premise of presenting the drug in the simplest formulation, containing the fewest excipients possible to ensure a stable medicine with an adequate shelf -life is the course that should be followed in the development process.
- Currently, delivery devices are usually metered-dose manual pump sprays, since these are cheap, robust and reliable but more sophisticated systems are now under development

Table 18.2 Considerations in formulating nasal preparations

Considerations	General	Budesonide aqueous nasal spray	Calcitonin nasal spray
Drug		Budesonide	Calcitonin Salmon
Dose of drug required		64 μg per spray (256 μg daily)	200 IU daily
Vehicle		Purified water	Purified Water
Volume of delivered dose	25–200 μL per nostril	50 μL (two actuations per nostril once a day or one actuation per nostril twice a day)	90 μL (one actuation per day into ONE nostril, alternate to other nostril following day)
Aqueous solubility of drug	Dictates whether suspension or solution is formulated	Practically insoluble in water (20 μg mL^{-1}), formulated as a micronized suspension	Completely soluble at required dose
Wetting agent	If suspension	Polysorbate 80	None
Solubilizer	If solution is required		Not required
Chelating agent	To optimize stability	Disodium edetate	None
Antioxidant	To optimize stability	Ascorbic acid	None
pH	pH should favour optimal drug stability, other considerations include: maximizing amount of drug in non-ionized form and avoidance of irritation of nasal mucosa	4.5 adjusted using hydrochloric acid, concentrated	3.5–4.5
Viscosity	Increasing viscosity increases residence time in the nasal cavity and reduces post-nasal drip	Dispersible cellulose (microcrystalline cellulose and carboxymethylcellulose sodium, 89:11, w/w)§	None
Tonicity	Should be adjusted to approximately the same osmotic pressure as that of the body fluids	Glucose, anhydrous	Sodium chloride
Preservative	Should be non-irritant	Potassium sorbate	Benzalkonium chloride
Humectant	To minimize irritation, e.g. glycerol		
Flavouring/ taste-masking agent	To improve taste as formulation is cleared to throat		
Delivery device	Drops or spray (aqueous bottle or metered dose)	Metered-dose, manual pump spray	Metered-dose, manual pump spray

Local delivery

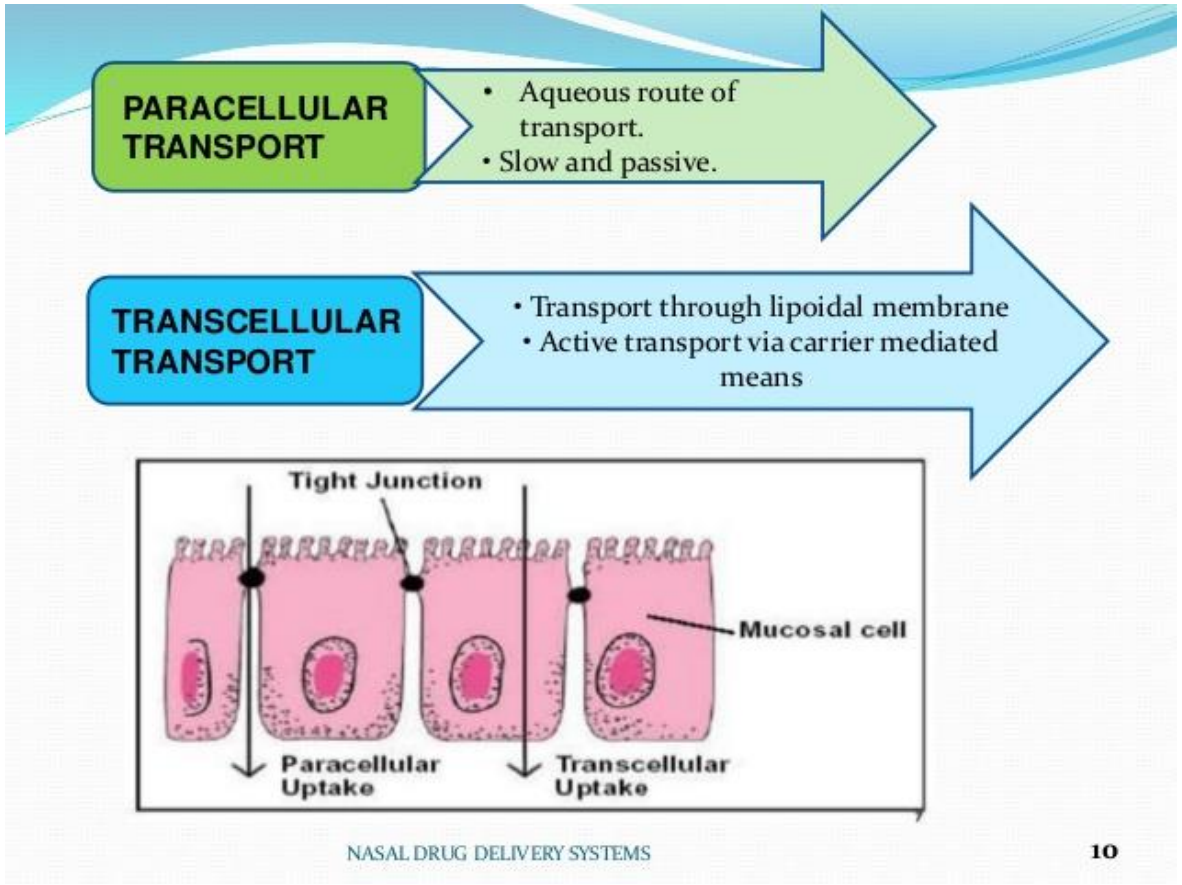
- For conditions affecting the nose, it is logical to deliver the drug directly to its site of action. This permits the rapid relief of symptoms with a much lower dose of drug than would be necessary if it were delivered by the oral route, and reduces the chance of systemic side effects. For example, this is particularly pertinent when delivering corticosteroids to reduce local inflammation of the nasal mucosa and sinuses, without causing pituitary-adrenal suppression, or alternatively when using localized antihistamine therapy without inducing drowsiness.

Systemic delivery

- The rationale or the use of the nasal cavity for systemic delivery includes its accessibility, avoidance of pre-systemic metabolism and potential to provide a rapid onset of action. Its use for peptides (Tables 38.1 and 38.2) has been successful since, although only a very low percentage of administered drug is absorbed (i.e. low bioavailability), the attained plasma levels are sufficient for therapeutic efficacy.
- Many of the marketed nasally administered peptides have wide therapeutic windows. Therefore, providing the minimum therapeutic level is exceeded in the bloodstream, a large variability in the final attained plasma level can be tolerated, without systemic toxicity becoming manifest.
- Any potential localized toxicity can be minimized in chronic administration by alternating nostrils when daily dosing (Table 38.2). Intranasal delivery can also be useful in emergency situations, such as in the treatment or opioid overdose (using naloxone) or in the treatment of intractable childhood seizures (using benzodiazepines).

Anatomical and physiological factors affecting intranasal systemic delivery

- For a drug molecule to enter the systemic circulation it must first be absorbed across the nasal epithelium.
- This may occur via the mechanisms of passive diffusion via the transcellular or paracellular routes. The transcellular pathway is the principal route of absorption for lipophilic molecules, while small, hydrophilic molecules diffuse between the epithelial cells (paracellularly) via the tight junctions which are dynamic structures responsible or the integrity of the nasal epithelium.
- This latter pathway avoids the need or the drug molecules to partition into and out of the lipophilic membrane of the epithelial cells, but imposes a size restriction of between 0.39–0.84 nm.
- Transcellular absorption can also occur via endocytosis, the route exploited by large hydrophilic molecules (>1 kDa), and via active transport mechanisms where drug molecules with a similar structure to a natural substrate can interact with a carrier protein to cross the epithelial cells.
- Since most drug absorption takes place by passive diffusion, the relatively large surface area of the nasal cavity and its rich blood supply (which helps to maintain the concentration gradient across the epithelium) aid this process. Working against these positive attributes of the nasal cavity are the barriers presented by mucus and the epithelium itself and the nasal clearance mechanisms including mucociliary clearance and metabolism. The advantages and disadvantages of the nasal cavity or systemic drug delivery are summarized in Table 38.3.



Active Transport: Endocytosis & Exocytosis

- Exocytosis: secretion of molecules outside the cell via a vesicle fusing to a membrane
- Endocytosis: engulfing of molecules inside the cell via vesicle formation

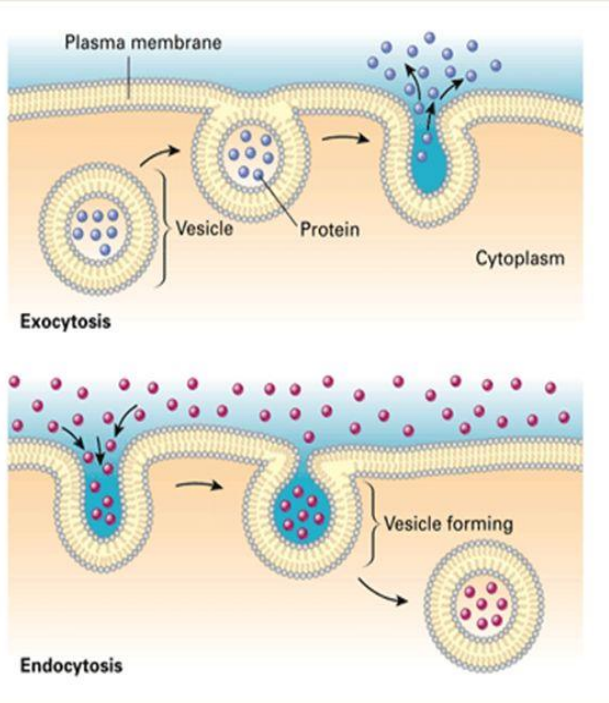


Table 38.3 Advantages and disadvantages of intranasal drug delivery for systemic activity

Advantages	Disadvantages
Large surface area for absorption (approximately 160 cm^2)	Limited to small delivery volumes (25–200 µL) therefore require potent drugs
Good blood supply and lymphatic system	Mucociliary clearance, mucus barrier
Avoids hepatic first-pass metabolism	Enzymatic activity (pseudo first-pass effect)
Epithelium is permeable to small, lipophilic drug molecules; rapid absorption and onset of action	Low epithelial permeability for hydrophilic drugs; require absorption enhancers and large doses
Non-invasive, so minimal infection risk during application and low risk of disease transmission (unlike parenteral route)	
Easy to self-administer and adjust dose	

Mucociliary clearance

- The main drug absorption site is the respiratory epithelium of the nasal turbinates, which is where mucociliary clearance dominates. Drug deposited anterior to this region will remain in the nasal cavity or longer than drug deposited in the turbinates, but absorption from this site is less.
- Once drug particles (if formulated as a suspension) or molecules (if in solution) find their way on to the mucociliary 'conveyor belt' they will be cleared from the nasal cavity and therefore have a limited contact time with the absorption site.
- For drugs which are in solution and rapidly absorbed (lipophilic, low molecular weight) the limited contact time is likely to be well in excess of that required or complete absorption. However, or drug particles needing time to dissolve prior to absorption, and or polar drug molecules with a low rate o absorption once in solution, the rate of mucociliary clearance is likely to play a significant role in limiting the extent of absorption.

Mucus barrier

- The nasal mucosa is protected from the external environment by a layer of mucus. In the nasal cavity this exists as a gel phase which is approximately 1–10 µm thick and found above a watery, sol phase surrounding the cilia (periciliary layer) which is about 7 µm deep (Fig. 38.1).
- Mucus is secreted continuously by the goblet cells and submucosal glands. Normal mucus is 97% water and 3% solids; with the latter comprising: i) mucins (about 30% of the solid content), ii) non-mucin proteins (e.g. albumin, immunoglobulins, lysozyme and lactoferrin), iii) inorganic salts and iv) lipids.
- Mucins are extremely large glycoproteins (up to 3 × 106 daltons per monomer) with protein regions rich in serine and threonine which are linked, by their hydroxyl side groups, to sugar chains (O-glycosylation). They are anionic (negatively-charged) because most of their terminal sugars contain carboxyl or sulphate groups. These glycosylated (sugar-rich) regions are separated by regions of non-glycosylated, 'naked' protein, rich in cysteine residues, which are believed to form globular domains stabilized by disulphide bonds.
- These 'naked' domains are the most hydrophobic regions of mucins and probably adsorb significant amounts of lipids. They are also the most antigenic sites on mucins. Entanglement of mucin polymers leads to the formation of a mucous gel and the generation of a mesh which is stabilized by non-covalent calcium dependent cross-linking of adjacent polymers.
- The sugar side chains bind large amounts o water allowing the mucus to act as a lubricant and a reservoir or the periciliary fluid within which the cilia beat. Mucus is a viscoelastic gel with properties of both a deformable solid (elasticity) and a viscous fluid. Cilia can only transport mucus of the appropriate viscoelasticity and this is controlled by the level of mucus hydration.

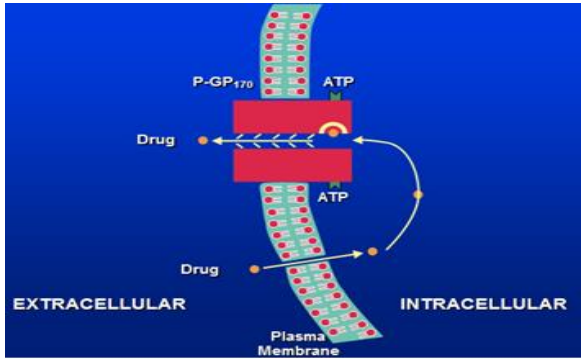
Mucus barrier-*continued*

- The presence of mucus at the epithelial surface of the nasal cavity provides an additional potential diffusion barrier to drug delivery. The ability of a molecule to diffuse through the gel is a function of the size of the drug molecule, the effective mesh size of the mucous gel formed by the mucin molecules and any interactions between the drug and the components of the mucous gel.
- The permeability of small, uncharged molecules appears to be less affected by a mucous barrier than the permeability of larger, cationic molecules. However, several large molecular weight, globular proteins (e.g. bovine serum albumin) and even 500 nm PEG nanoparticles have been observed to readily diffuse through mucus (cervical) at a rate comparable to their diffusion through water.
- Mucus seems to present a barrier to the permeability of small, relatively hydrophobic molecules like testosterone and this is believed to result from their interaction with the lipid component of the mucous gel or the hydrophobic (non-glycosylated) region of the mucin molecules.
- It is thought that such small molecules are only able to form low-affinity, monovalent bonds with the mucins which persist or just a short time. A number of studies indicate that positively-charged (cationic), low molecular weight drugs, such as amikacin, gentamicin, tobramycin and some β-lactam antibiotics bind electrostatically to negatively charged components in mucus. It is believed that such molecules bind tightly and polyvalently to the negatively-charged sugar residues o the mucins. Large positively-charged nanoparticles, such as those coated with chitosan bind especially tightly to mucous gels by a similar mechanism.

Enzymatic activity

- A broad range of enzymes are present in the nasal cavity, including those involved with Phase 1 metabolism (e.g. monooxygenase, carboxyl esterases,epoxide hydrolases and cytochrome P450 isoenzymes) and also conjugative Phase II metabolism (e.g. UDP-glucuronyltransferase and glutathionetransferase).
- In addition, proteolytic enzymes (proteases and aminopeptidases) provide a potential barrier to the absorption of certain peptides. Drugs may be metabolized in the lumen of the nasal cavity or as they pass across the nasal epithelium.
- However, the metabolic activity of the nasal cavity is less than that of the gastrointestinal tract (on a nmol/ mg protein basis) and, in addition, there are a number of factors that will affect the relevance of metabolism to drug absorption. These include, the amount of drug applied to the contained nasal surface area, the chemical nature of the drug, the rate of removal of drug from the cavity and its rate of absorption across the mucosa.

Epithelial barrier–efflux transporters



- The absorption of certain drugs across the nasal epithelium can be limited by the presence of efflux transporters. One such transporter, belonging to the super family of adenosine triphosphate (ATP)-binding cassette (ABC) transporters has been found in the nasal respiratory mucosa and is termed P-glycoprotein 1 (P-gp), multi-drug resistance protein 1 (MDR1) or ABCB1. This transporter is also expressed by cells within the intestine and poses a similar barrier to drugs that are orally administered.
- P-gp is a 170 kDa glycosylated transmembrane protein found in the apical membranes of the cells. It is able to bind a wide variety of hydrophobic and amphiphilic substrates, including certain peptides, to its binding site located cytoplasmically at the inner leaflet of the apical cell membrane and actively pump them from the cell, back into the nasal cavity.
- Hence, drugs that are substrates for P-gp will be less well absorbed across the nasal epithelium than their physicochemical properties (molecular size, lipophilicity, degree of ionization) might predict. Active transport is concentration-dependent, saturable and can be competitively inhibited by other substrates or the binding site. Thus, co-administration of an inhibitor of P-gp, such as rifampicin or verapamil can enhance drug absorption. P-gp is also found in the olfactory epithelium, at a higher concentration than is found in the respiratory epithelium, where it reduces drug absorption into the brain.

Physicochemical properties of drugs affecting intranasal systemic delivery

- In general, for a drug to be absorbed it must be in solution (molecularly dispersed). Since the volume of liquid that can be administered intranasally is relatively low (25–200 µL) drugs with low aqueous solubility and/ for those requiring a high dose can be problematic. Such issues can be overcome by formulating the drug as a suspension or powder (generally in the micrometre size range), in which case the drug will be required to dissolve in the fluid of the nasal cavity prior to absorption. There is some evidence that nanoparticles (which are an order of magnitude smaller) can be transported from the nasal cavity into the systemic circulation without dissolving. These properties are:

➢Solubility

➢Lipophilicity/hydrophilicity and molecular size

➢Degree of ionization

Solubility

- Strategies to increase the solubility of a drug can involve modifying the molecular form and include the use of prodrugs and choice of salt form, or the use o appropriate excipients, such as co-solvents, when the drug is formulated (considered below).
- Prodrugs are often developed to increase the lipophilicity of a drug molecule and hence its absorption across a biological membrane. However, in the case of nasal delivery the principle has been explored to increase the aqueous solubility of the parent drug to enable a clinically relevant dose of drug to be dissolved in less than 150 µL of solution and has been successful or several drugs.
- For instance, the solubility of L-dopa (aqueous solubility =1.65 mg mL−1) is increased 400 old by producing it as a butyl ester prodrug, enabling an effective dose of 10 mg to be delivered in 125 µL. The prodrug is rapidly converted to the active parent drug once it enters the bloodstream.
- The appropriate choice of salt form of an ionizable drug can be used to increase its aqueous solubility. This is an empirical process since it is hard to predict reliably the effect of a particular counter ion on the solubility of the resulting salt. Nevertheless, examples exist where this approach has been successful. For instance, the solubilities of galantamine hydrobromide and morphine sulphate have been increased sufficiently by exchanging the bromide or sulphate ions or gluconate to make nasal delivery feasible or these compounds. However, a change in salt form can result in irritancy to the nasal mucosa and this has to be considered when choosing an appropriate counter-ion.

Lipophilicity/hydrophilicity and molecular size

- Once in solution, lipophilic drugs such as propranolol, progesterone and fentanyl are rapidly absorbed from the nasal cavity by the transcellular route and have a nasal bioavailability similar to that obtained after intravenous administration (almost 100%).
- The absorption of hydrophilic (polar) drugs occurs via the paracellular route (between the epithelial cells via the tight junctions) and the rate and extent of absorption is inversely proportional to the molecular weight of the drug.
- Since the paracellular route provides a much smaller area or absorption than the transcellular route (the paracellular route comprises about 0.01% o the transcellular route in the gastrointestinal tract), the absorption of hydrophilic compounds is much slower than that of lipophilic drugs.
- For both lipophilic and hydrophilic molecules, absorption is relatively efficient or drugs with a molecular weight below 1 kDa but then declines. Nevertheless, calcitonin (salmon) is successfully used to reduce the risk o vertebral fractures in postmenopausal osteoporosis (Table 38.2) despite being a hydrophilic peptide with a molecular weight of 3432 Da and having a nasal bioavailability that is just 3% of its bioavailability when delivered intramuscularly.
- When considering dose reproducibility from the nasal cavity, dosing is relatively consistent or low molecular weight drugs when compared to the oral or parenteral routes, whereas or compounds with a high molecular weight, such as peptides and proteins, relatively high variability is exhibited compared to injections.

Degree of ionization

- For drugs that are weak acids or bases, the pH of the nasal cavity will affect the degree of ionization of the drug. The pH at the surface of the nasal mucosa has been reported to be 7.4 while the pH of the mucus is in the range 5.5–6.5.
- In addition, the pH of the formulation itself can alter the local pH, particularly in buffered vehicles are employed. Studies have indicated that the non-ionized form of a drug, which has a higher partition oil/ water partition coefficient than its ionized counterpart, is better absorbed than the ionized form (pH partition hypothesis) The ionized form of the drug also shows some permeability, the degree of which may be dependent upon the nature of the counter-ion.

Formulation factors affecting intranasal Systemic delivery

- The same general formulation considerations apply to drugs formulated or systemic action as or local action. However, additional strategies can be employed to increase absorption across the nasal epithelium. In essence, the bioavailability of nasally administered drugs can be limited by:

➢ low aqueous solubility

➢ rapid and extensive enzymatic degradation of the drug in the nasal cavity

➢ short contact time between the drug and the absorptive epithelium of the turbinates due to mucociliary clearance

➢ poor permeability of the drug across the respiratory epithelium.

- Approaches that have been used to overcome these limitations are summarized in Table 38.4 and include the use of prodrugs ,enzymatic inhibitors, mucoadhesive formulations and permeation enhancers which affect the epithelial barrier.

Table 38.4 Common problems associated with poor nasal bioavailability and possible solutions

Problem	Challenge	Possible solutions
Low aqueous solubility of drug	Improve aqueous solubility of drug	Prodrugs Co-solvents Cyclodextrins Novel drug delivery systems
Enzymatic degradation of drug	Reduce affinity of drug for nasal enzymes Inhibit nasal enzymes Limit access of nasal enzymes to drug	Prodrugs Enzyme inhibitors Encapsulation, e.g. liposomes, microspheres, nanoparticles
Short contact time	Increase residence time of drug in turbinates	Increase viscosity of formulation Use mucoadhesive formulations
Low permeability across the nasal epithelium	Increase permeability Increase solubility	Prodrugs (with increased lipophilicity) Prodrugs (with increased hydrophilicity) Co-solvents Cyclodextrins Novel drug delivery systems
	Modify nasal epithelium	Permeation enhancers

Increasing aqueous solubility

- Drug solubility can be increased by using a mixed solvent system or a co-solvent in the formulation. Solvents used with water or nasal delivery include glycerol, ethanol, propylene glycol and polyethylene glycol (PEG).
- PEG 300 has been used successfully to increase the solubility of buprenorphine hydrochloride and melatonin, and has enabled clinically relevant doses to be administered with low nasal irritation being observed in humans.
- Cyclodextrins are cyclic compounds composed of α-D -glucopyranose units. They tend to be water-soluble due to their hydrophilic/polar outer surface, but have a hydrophobic/ less polar centre. They are able to increase the aqueous solubility o lipophilic compounds by forming dynamic inclusion complexes where the lipophilic part of the drug molecule is incorporated into the lipophilic central cavity of the cyclodextrin ring. An intranasal formulation containing 17-β-estradiol solubilized in dimethyl-β-cyclodextrin (seven glucopyranose units) was available for the treatment of menopausal symptoms, until it was withdrawn in 2006.

pH of the formulation

- Many drugs are weak acids or bases and their degree of absorption will depend on their pKa and the pH of the absorption site. The pH of a formulation is generally dictated by the stability of the drug but, within these constraints, a pH flavouring more unionized molecules would be expected to enhance absorption. It is important to recognize that the formulation should be non-irritant to the nasal mucosa and formulating at a pH close to that of the nasal cavity (5.0–6.5) may also be desirable although, unexpectedly, it has been shown that pH values ranging from 3–10 can be tolerated by the nasal mucosa.

Use of enzyme inhibitors

- Proteolytic enzyme inhibitors could prevent the hydrolysis o peptide and protein drugs in the nasal cavity improving their stability at the absorption site. As examples, the aminopeptidase and trypsin inhibitor, camostat mesilate, improved the nasal absorption of the peptide vasopressin and its analogue, desmopressin, and the absorption of calcitonin can also be enhanced by the use of trypsin inhibitors.
- However, proteolytic enzyme inhibitors do not improve the ability of peptide and protein drugs to cross the epithelium o the nasal cavity and there ore do not dramatically improve nasal bioavailability.

Increasing nasal residence time

- One way of increasing the time that the formulation is in contact with the absorptive mucosa is by the use o mucoadhesive polymers, such as cellulose derivatives, polyacrylates, starch and chitosan. Most of these polymers are 'Generally Regarded As Safe', The polymers themselves are not absorbed and there ore would not be expected to cause any systemic toxicity. Mucoadhesives can increase absorption by three mechanisms:

- Optimum hydration will promote the extension of polymer chains which will interact with the nasal tissue and resist the removal of the formulation by mucociliary clearance, thus increasing its retention time in the nasal cavity
- acting as carriers, they can reduce the contact between the drug and the enzymes of the nasal mucosa and protect the drug from any potential degradation
- some polymers can affect the tight junctions between the epithelial cells. As the polymer becomes hydrated it causes dehydration of the epithelial cells which can temporarily open the tight junctions, so increasing permeability of the epithelium to drugs using the paracellular route.

Increasing nasal residence time-*continued*

- Examples of polymers and drugs that have been used in studies of nasal mucoadhesion are given in Table 38.5. When the polymers are formulated in solution, the viscosity of the preparation will be greater than that of a simple solution. Whilst an increased formulation viscosity leads to a prolonged residence time, it does not always result in increased absorption.

Table 38.5 Mucoadhesive polymers proposed/employed for nasal delivery

Polymer type	Examples of mucoadhesive polymers studied	Dosage forms	Examples of drugs studied
Cellulose derivatives (soluble)	Hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose	Gel Powder Liquid	Apomorphine Insulin Ciprofoxacin
Cellulose derivatives (insoluble)	Ethyl cellulose, microcrystalline cellulose	Powder Spray	Leuprolide Calcitonin
Polyacrylates	Carbopol 971P, Carbopol 934P, Carbopol 981P	Powder Liquid Gel	Apomorphine Metoclopramide
Starch	Drum-dried waxy maize starch Degradable starch microspheres Starch nanoparticles Starch microspheres	Liquid Powder	Apomorphine Desmopressin Gentamicin Human growth hormone Insulin Metoclopramide
Chitosan	Chitosan Chitosan microspheres Chitosan glutamate	Liquid Powder	Insulin Human growth hormone Morphine HCl Gentamicin Metoclopramide
Pectin	Low methoxyl (LM) pectin (PecSys™)	Liquid turning to gel in situ	Fentanyl (PecFent™)

Increasing nasal residence time-*continued*

- To overcome this problem a type of gel has been developed (in-situ gel) that is liquid prior to administration (allowing convenient and accurate dosing) but forms a gel once in contact with the nasal mucosa. A marketed product (PecFent™) containing the analgesic fentanyl and low methoxyl (LM) pectins is administered to the nasal cavity as a solution, but interacts with calcium ions in nasal secretions to form a muco/bioadhesive gel.

Enhancing the permeability of nasal epithelium

- It is possible to increase the absorption of both small and large hydrophilic drug molecules by administering them with permeation enhancers which modify the structure of the nasal epithelium. However, it is important that any alteration to the barrier function of the epithelium is short-term and reversible, since the epithelium constitutes one of the body's primary defence mechanisms against insult rom the external environment. A range of nasal products is on the market, none of which contains a permeation enhancer.
- This is because the drug molecules are either both small and lipophilic, and have adequate absorption without the need or a permeation enhancer, e.g. sumatriptan, entanyl and nicotine, or because the nasal bioavailability, although low, is still sufficient or the drug to exert a therapeutic effect, as is the case or the peptides calcitonin, desmopressin, buserelin and naferelin.

Enhancing the permeability of nasal epithelium

- The requirements of an ideal permeation enhancer include the following:

➢ rapidly-acting with a transient and reversible effect on the nasal epithelium

➢ not absorbed systemically.

➢ non-toxic, non-irritant and non-allergenic.

➢ does not permit entry of dangerous environmental material.

➢ compatible with drugs and other excipients in the formulation.

➢ safe or chronic use (depending on the condition to be treated).

Table 38.6 Examples of permeation enhancers

Type of permeation enhancer	Examples	Proposed mechanism(s) of action	Toxicity
Cationic polymers	Chitosan Poly-L-arginine Cationized gelatin	Ionic interaction with negatively-charged nasal epithelium and nasal mucus Transiently opens tight junctions Bioadhesion	Well-tolerated Negligible mucosal damage
Cell-penetrating peptides (also called protein transduction domains)	Penetratin Octa-arginine	Various hypotheses which are largely unsupported	Variable
Cyclodextrins	Modified derivatives	Protection from enzymatic degradation either directly or by shielding susceptible portions of molecules in hydrophobic cavity Removal of lipids from cell membranes leading to increase in membrane permeability Change distribution of tight junctions causing increased paracellular permeability Interaction of cyclodextrins with hydrophobic portions of large molecules, e.g. peptides and proteins can improve their permeability	Considered safe
Tight junction modulating lipids	Glycosylated sphingosines Alkylglucosides Oxidized lipids Ether lipids	Interaction with lipid raft associated with tight junctions to modulate their properties	Alkylglucosides are cytotoxic

Nasal vaccines

- Mucosal tissues are attractive sites or vaccination due to their accessibility, immunological competence and because local immune responses can be elicited which can protect against infection at the point of virus entry. Intranasal vaccination targets the nasal-associated lymphoid tissue (NALT) which is situated beneath the nasal epithelium and consists of groups of dendritic cells, T-cells and B-cells.
- So far, the intranasal route has been successfully used (Table 38.1) for a commercial influenza (live-attenuated) vaccine (FluMist™).
- The benefits of nasal vaccination when compared to needle-based delivery systems include a reduced risk o needle-stick injuries and risk of infection from the re-use of needles, increased patient compliance among patients with needle phobia, a decreased need or vaccines to be administered by trained healthcare professionals and possibly a decreased need or cold chain storage and distribution, if vaccines can be formulated as dry powders.

CNS delivery

- The blood-brain barrier (BBB) restricts the entry of potentially harmful substances into the brain but also limits the access of potentially useful drugs.
- It exists at the level of the cerebral microvasculature. In contrast to the leaky barrier presented by the endothelial cells of the capillaries in the peripheral circulation, the endothelial cells in the brain exhibit low rates of pinocytosis and are joined by tight junctions which limit the paracellular diffusion of hydrophilic solutes from the blood into the brain.
- In addition, the BBB expresses a high number of efflux transporters, such as P-glycoprotein (P-gp), which further reduce access to the brain or those molecules that might be predicted to be well-absorbed from their size and lipophilicity.

CNS delivery

- Drugs delivered intranasally that enter the systemic circulation would have to cross the BBB to enter the CNS. However, it has been proposed that there is a route from the olfactory region of the nasal cavity (Fig. 38.1) to the brain that avoids the BBB and which can be exploited to deliver drugs directly to the brain.
- This is currently an area of great research interest and studies have shown that both low molecular weight drugs and high molecular weight peptides and proteins appear to be able to access the brain following intranasal deliver
- It should be noted that in the many studies of drug transport (low molecular weight drugs and peptides and proteins) from the nose to the brain, the amount of drug reaching the CNS is small compared to the amount administered to the nasal cavity, generally less than 1%.
- One major problem is the inaccessibility of the olfactory region of the nasal cavity coupled with the poor permeability of certain types of molecule (including peptides and proteins) across the olfactory epithelium. There is a need or a formulation containing an acceptable nasal permeation enhancer and a bioadhesive material which can be delivered from a nasal device that is able to target the formulation to the olfactory region.

Nasal delivery systems

- Nasally administered medicines can be formulated as ointments or creams but most usually as a liquid (solution, gel or suspension) or as a powdered solid (Tables 38.1 and 38.2).
- multi-dose liquid dosage forms can require the inclusion of antimicrobial preservatives to prevent the growth o contaminating microorganisms. There is evidence that some of these preservatives can cause irritation to the nasal mucosa and/or damage the cilia and there ore compromise mucociliary clearance, especially if used over a long period.
- Strategies to minimize or obviate such effects include the use of alternate nostrils, if chronic daily dosage is required, and the use of pressurized containers or unit-dose delivery systems (Table 38.8) which do not require the inclusion of a preservative.

Nasal delivery systems

- There is a move towards delivery systems that deliver an accurate metered dose and away rom dosage forms such as nasal drops, which require considerable skill, dexterity and even flexibility (in terms of mobility) to apply uniformly across the mucosa. Smaller doses (< 100 µL) tend to persist longer than larger doses which may drip rom the nostril after delivery.
- Powdered solids tend to remain in the nasal cavity for longer periods than liquids, since a preliminary hydration step generally occurs before mucociliary clearance reaches maximal efficiency. This can prolong the window over which systemic drug absorption can occur or the duration o action o a locally-acting drug.
- Creams and ointments can also be utilized to prolong retention in the cavity. Moreover, the use of solids or creams limits the rapid introduction of fluid to the throat and mouth, which can often initiate an unwelcome taste and possibly induce coughing and gagging. Control of particle size is important since particles with sizes less than 10 µm can move beyond the nasal turbinates towards the lung, whereas particles larger than 50 µm can be cleared more rapidly by mucociliary clearance and nose blowing.

The End