Advanced Pharmaceutical Technology

Introduced by:

Dr. Ahmed NA

University of Basrah / College of pharmacy

Nasal Drug Delivery

Outlines:

- Introduction
- Advantages and limitations
- Anatomy and physiology
- Drug travel from dosage form to target
- Drug properties and nasal route
- Dosage form and DDS.s

Introduction

- **The most common reason for introducing a drug into the nasal cavity is to provide a convenient and accessible route or rapidly and efficiently managing the localized symptoms associated with allergic rhinitis, nasal congestion and nasal infection.**
- **The intranasal route has also been exploited for the delivery of drugs (specially proteins) to the systemic circulation. (why?)**

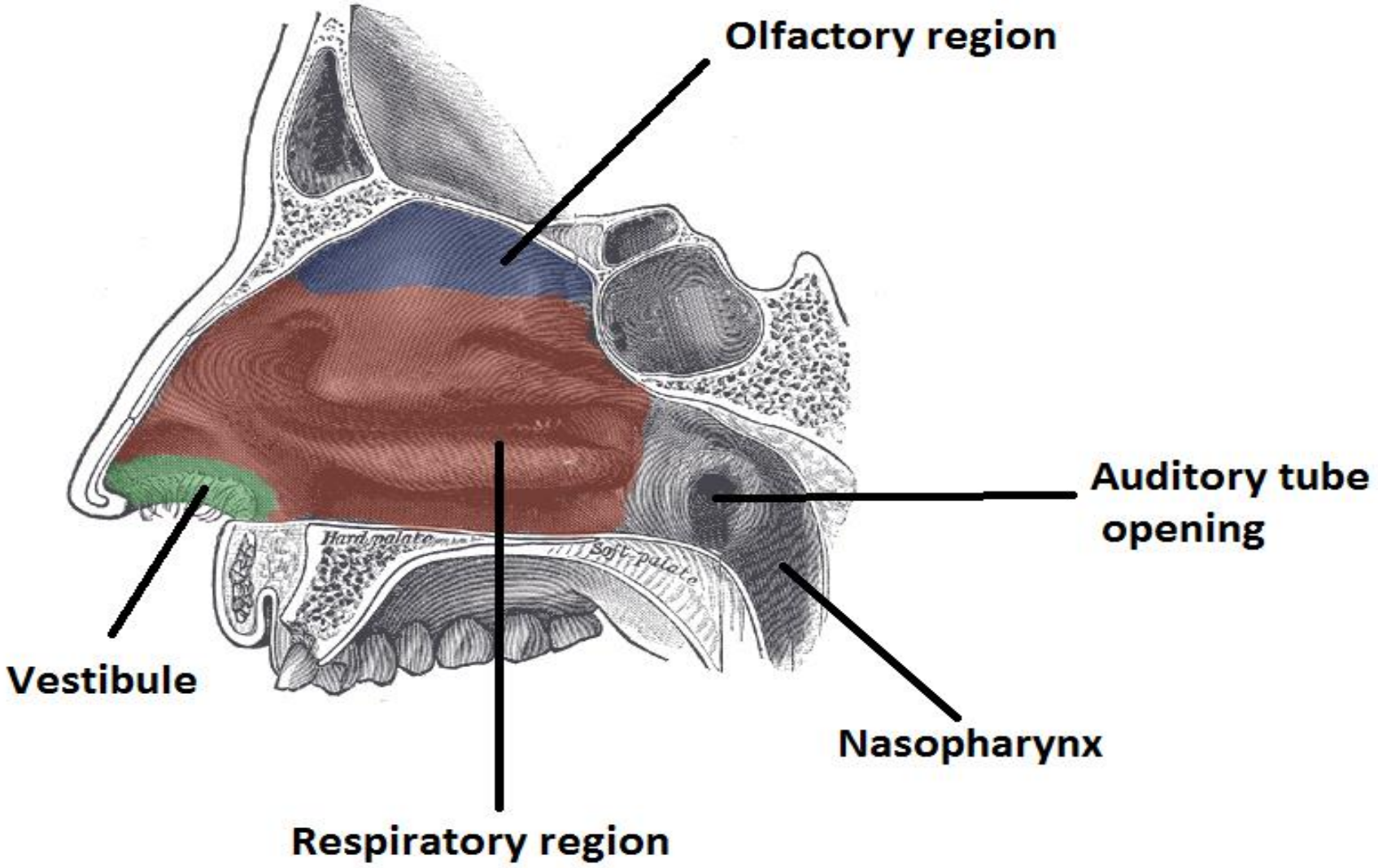
Table 38.3 Advantages and disadvantages of intranasal drug delivery for systemic activity

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	

Other limitations

- Nasal irritation.
- More toxicity possibility in presence of absorption enhancers.
- There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa.
- Difficulty in administration by some patients.
- Nasal disease may reduce drug bioavailability.

Anatomy and physiology



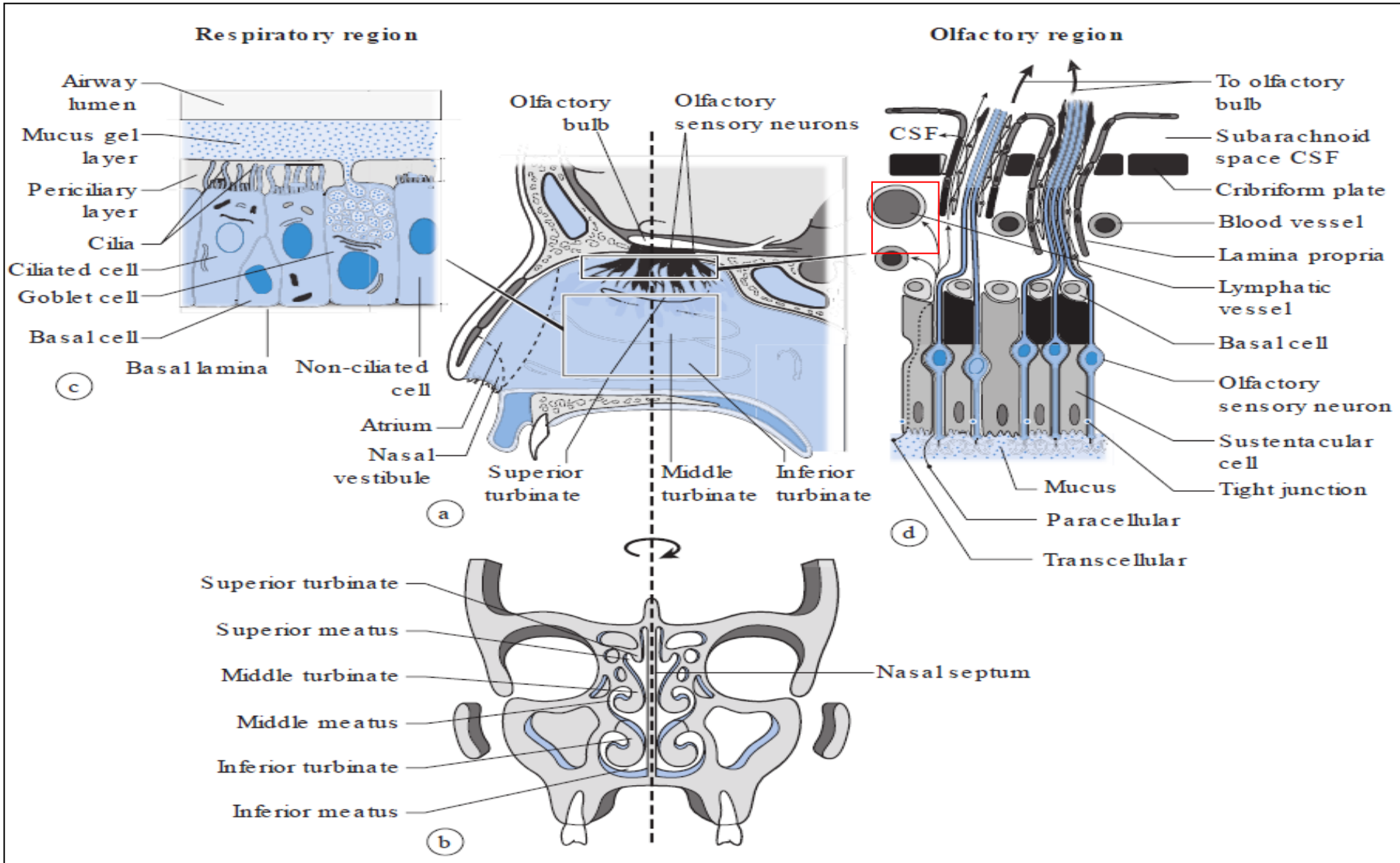


Figure 38.1 • Lateral wall of the nasal cavity (**a**) and cross-section through the middle of the nasal cavity (**b**). The respiratory epithelium (**c**) and the olfactory epithelium (**d**).

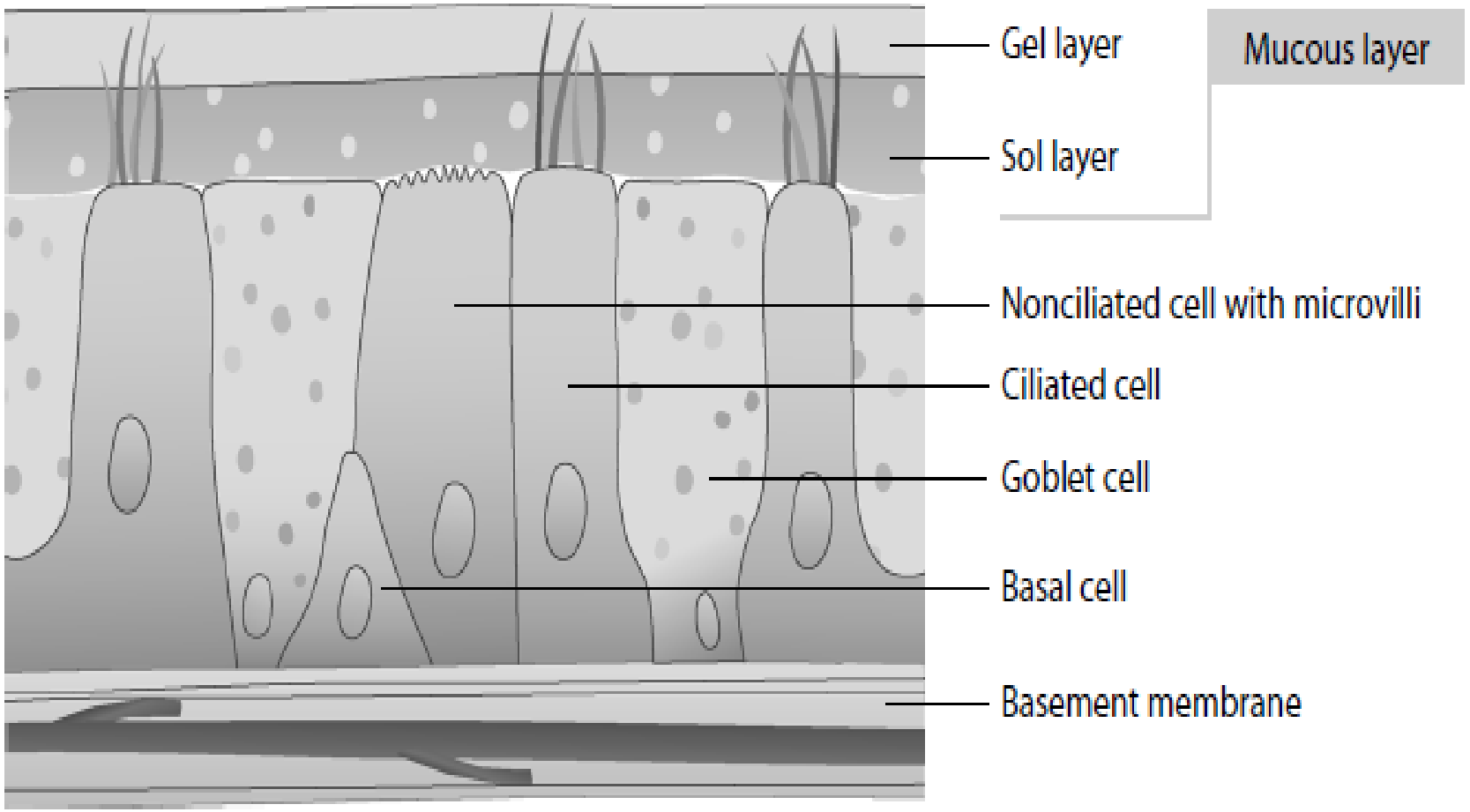


Fig. 2. Cell types of the nasal epithelium with covering mucous layer.

- The nose is a complex multifunctional organ.
- It represents a most efficient first line of defense for the body's airway (As filter).
- With an efficient absorption surface for topically applied drugs.
- The rich vascular plexus of the nasal cavity provides a direct route into the blood stream for medications that easily cross mucous membranes.

- There is a relatively small volume of fluid in the nose at any one time, from 0.2 to 1.1 ml.
- The pH of the nasal epithelial cells is 7.4, but the mucus that drug particles encounter first is acidic, pH 5.5–6.5.
- Liquid formulations are generally cleared from the nose entirely in 30 minutes.
- Drug metabolizing enzymes in the nose include a number of cytochrome P450 isozymes, peptidases and esterases.

Drug travel from dosage form to target

1) Release

Nasal solutions and suspensions may be applied to the nose as drops or sprays.

Powders as well as solutions and suspensions may be administered with metered dose devices that provide a more precise dose than a multi-dose squeeze bottle.

- A few drugs have been formulated as gels or ointments for nasal administration to provide longer contact time with the membrane.
- The volume of the dose administered intranasally should be limited to 200 µL (100 µL per nostril) because the excess is lost either from the front or the back of the nasal cavity.

2) Absorption

- The nasal respiratory epithelium is difficult to access because it is behind the nasal valve. Drug doses are rapidly removed from the nose by mucociliary clearance.
- Drugs applied to the nose are absorbed by passive diffusion through the epithelium of the respiratory or olfactory areas which comprise the posterior two-thirds of the nasal cavity.

- An aqueous route of transport, which is also known as the paracellular route but slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble com-pounds.
- Drug also cross cell membranes by an active transport route via **carrier-mediated** means or transport through the opening of tight junctions.

For examples: chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport.

3) Distribution

- The capillaries of the respiratory epithelium drain into the sphenopalatine, facial and ophthalmic veins and then into the internal jugular.

Drug properties and the nasal route

- Pharmaceutical product development is a crucial task which is directly dependent on its therapeutic objectives.
- Therefore, before product development, important biopharmaceutical aspects need to be considered- firstly, whether it is intended for:

I- Localized delivery

II- Systemic delivery

III- Single or repetitive administration

- Local drug receptors include the histamine receptors in vascular endothelial cells, mast cells in connective tissue near blood vessels, and alpha adrenergic receptors on vascular smooth muscle. Corticosteroids need to reach intracellular receptors on endothelial cells in nasal vessels, as well as local fibroblasts, basophils, macrophages and lymphocytes.
- Intranasal influenza vaccine is targeted at nasal-associated lymphoid tissue in the pharynx.

- Drugs applied for systemic effect need to reach opiate and serotonin receptors in the brain, calcitonin receptors in bone and kidney, and vasopressin receptors in renal collecting ducts.

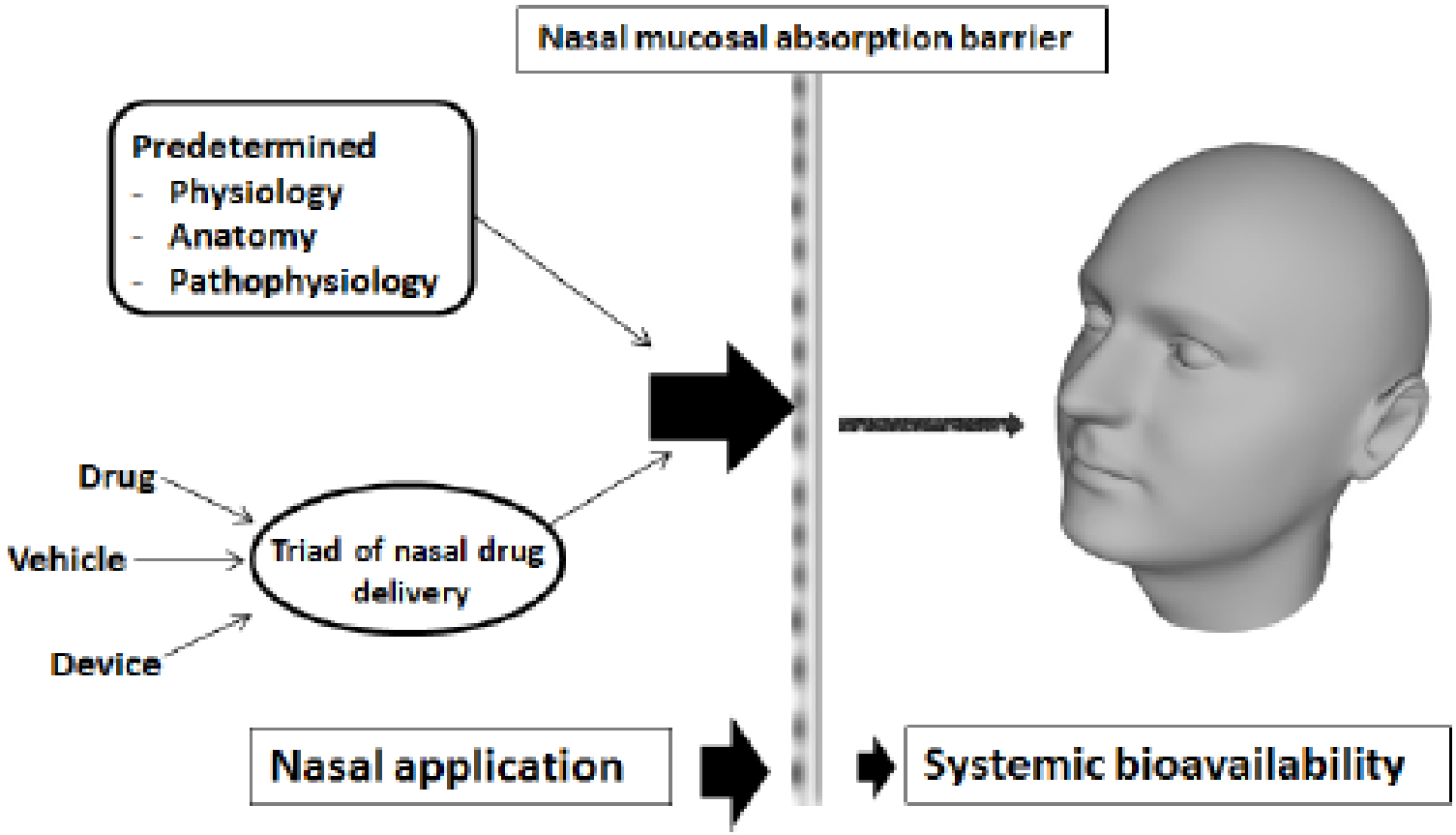


Figure 3. Consideration of formulation elements of nasal product development

These considerations are related to physiological and pharmaceutical factors.

- **Physiological factors can be summarized as follows:**

1) Effect of deposition on absorption.

2) Nasal blood flow

3) Effect of enzymatic activity.

4) Effect of mucociliary clearance.

5) Effect of pathological condition.

6) Mucus barrier and its interactions with some drugs??

7) Epithelial barrier –efflux transporters.

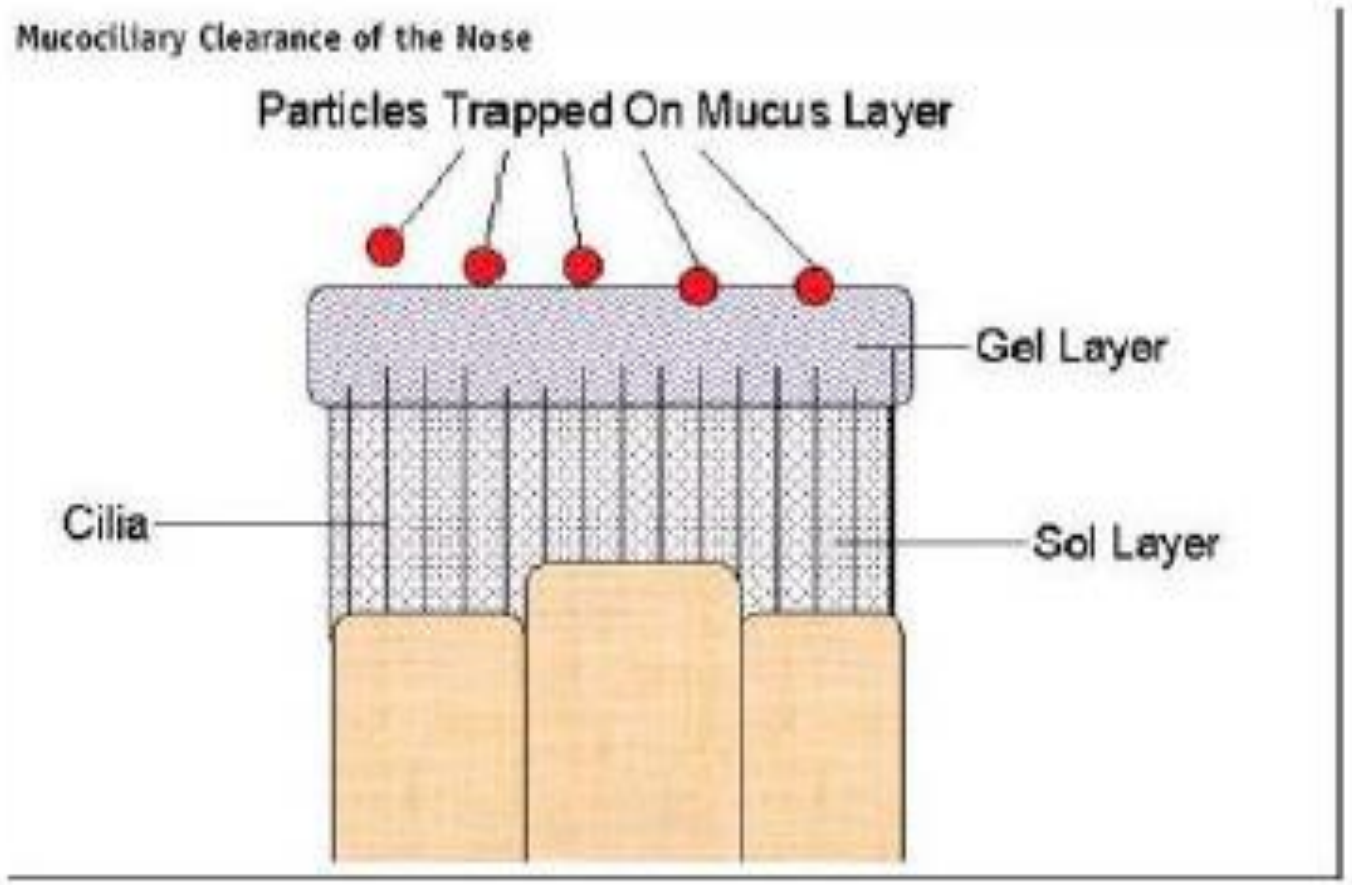


Fig 3 Effect of mucociliary clearance on nasal drug absorption.

Pharmaceutical factors:

- Divided into two sub-types:

Preformulation factors and formulation factors

- **Pre-formulation factors are related to the physicochemical properties of drug like:**

1) Molecular weight:

A linear inverse correlation with absorption up to 300 Dalton. decreases significantly if > 1000 Dalton except with the use of absorption enhancers.

2) Molecular shape, Linear molecules have lower absorption than cyclic shaped molecules.

3) Lipophilicity (preferred, logP <5).

4) Chemical nature, protein or not

5) Chemical form: base form, salt or ester

6) Particle size, greater than 10μm are deposited in the nasal cavity.

7) Polymorphism

8) Solubility and dissolution rate

9) pKa

10) potency <5 mg/dose

Formulation factors:

1) pH of the formulation:

Minimal nasal irritation is minimized and more lysozymes activity at pH 4.5- 6.5.

2) Volume and concentration:

The delivery volume is limited by the size of the nasal cavity.

An upper limit of 25 mg/dose and a volume of (25 to 200 µL/ nostril) have been suggested.???

3) Osmolarity and Buffer capacity (dilution effect can alter pH).

4) Excipients compatibility:

- Viscosity enhancers. Like ??
- Solubilizers (SAA or cyclodextrins, Co solvent like glycols, small quantities of alcohol…).
- Preservatives (mercury containing preservatives have a fast and irreversible effect on ciliary movement and should not be used in nasal systems).
- Antioxidants and humectants.

5) Application Device, affected by different factors like?????

Table 15.3 Ingredients for nasal products

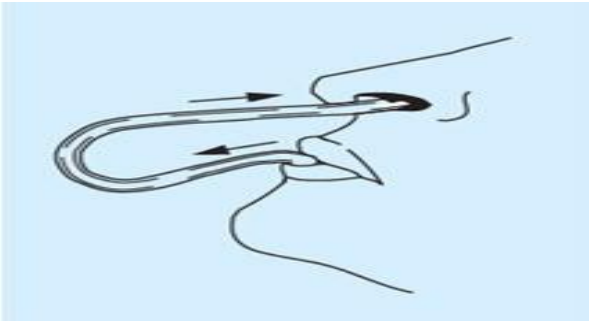
Category	Contribution
Solvents	Dissolution
Cosolvents	Dissolution, manageable size dose, viscosity
Ointment base	Semisolid nonaqueous vehicle with good retention
Wetting agents	Physical stability
Tonicity agents	Comfort. Some drug solutions are hypertonic and will require no tonicity agent
Buffers	Chemical stability (preferred pH between 5 and 8)
Antimicrobial preservatives	Microbial stability for all multi dose products containing water
Antioxidants	Chemical stability for oxidizable drugs
Propellants	Release drug in small droplets to enhance accessibility to respiratory membrane
Mucoadhesive viscosity enhancers	Increase retention at the site of administration. Convenience
Penetration enhancers	Increase permeability of absorbing membrane

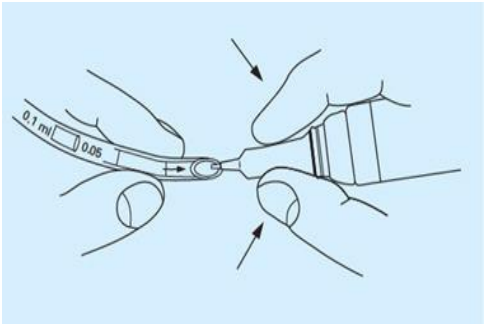
Table 38.4 Common problems associated with poor nasal bioavailability and possible solutions

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 Modify nasal epithelium	Prodrugs (with increased lipophilicity) Prodrugs (with increased hydrophilicity) Co-solvents Cyclodextrins Novel drug delivery systems Permeation enhancers

The dosage forms and DDS.s

- Nasal drops (with a pipette or a squeezy bottle, mainly local).
- A rhinal tube is a thin catheter that is loaded with a dose of the nasal solution from a squeezable dropper. One end of the tube is placed in the nostril and the other end is placed in the patient's mouth.





- Nasal sprays are metered dose devices (with or preservative free type) may be mechanical or propellant-driven type.
- Nasal gels or In situ gels.
- Nasal suspensions and emulsions, a nano-suspension formulation may be used to target the brain through the nose.

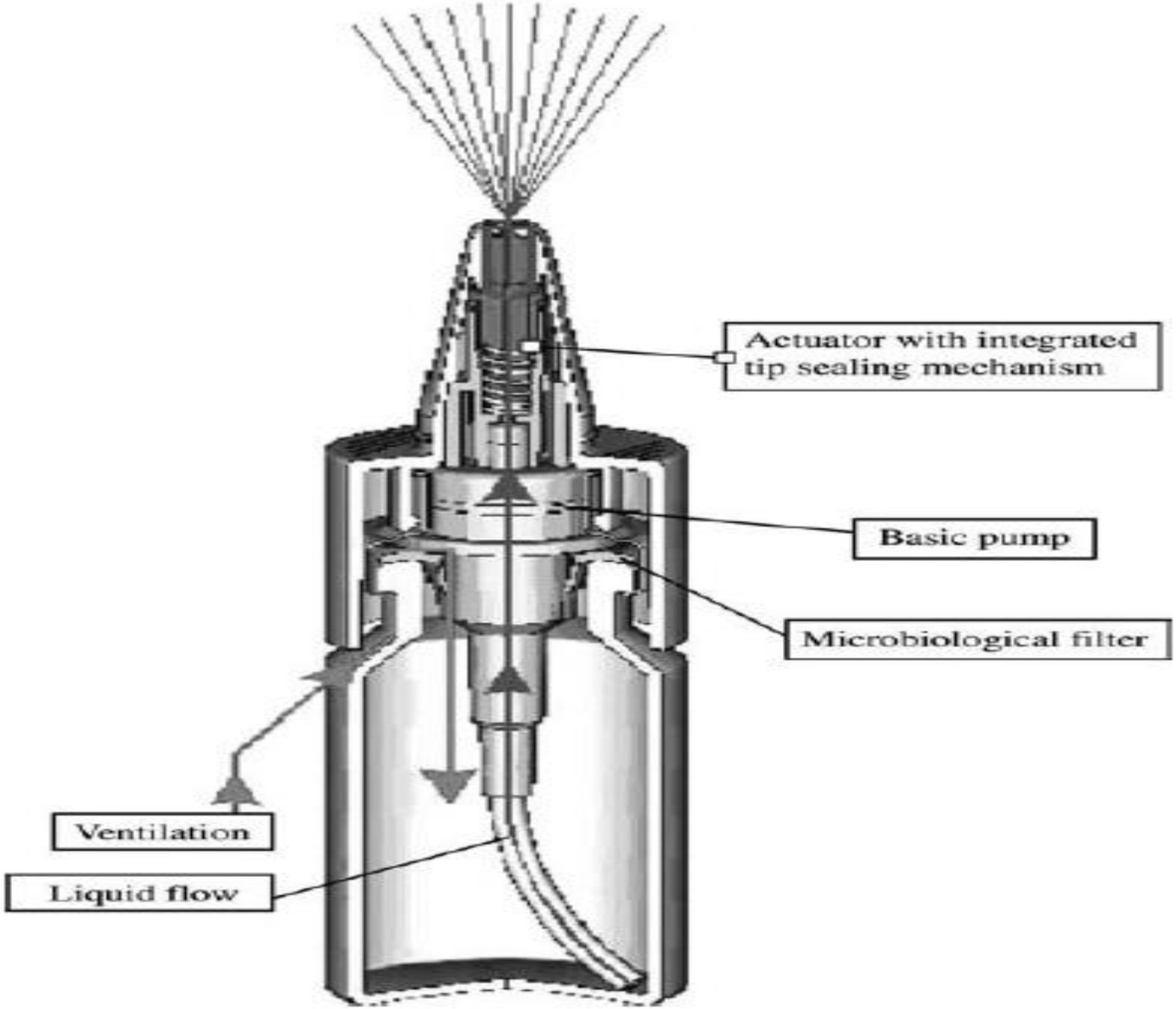


Fig. 7 Preservative-free system.

- Nasal micellar, liposomal and proliposomal* formulations. Specially for proteins and peptides.

Proliposomes are dry, free-flowing granules composed of sorbitol as carrier and lipids that form a liposomal dispersion on contact with water.

Their advantages are the combination of a fast onset (surface drug) and prolonged drug action (encapsulated drug) as demonstrated for propranolol and nicotine.

- Nasal Powders (spray dried, freeze dried), with bio-adhesive polymers, forming gel upon application.
- Nasal Microparticles
- Nasal microemulsions??

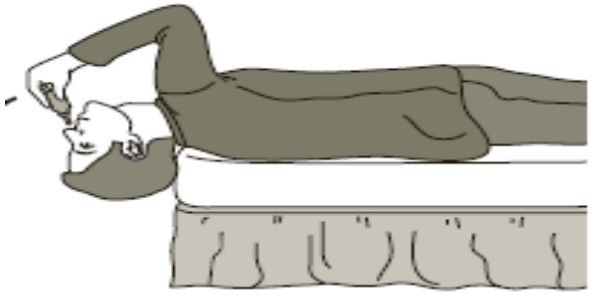
Counseling patients

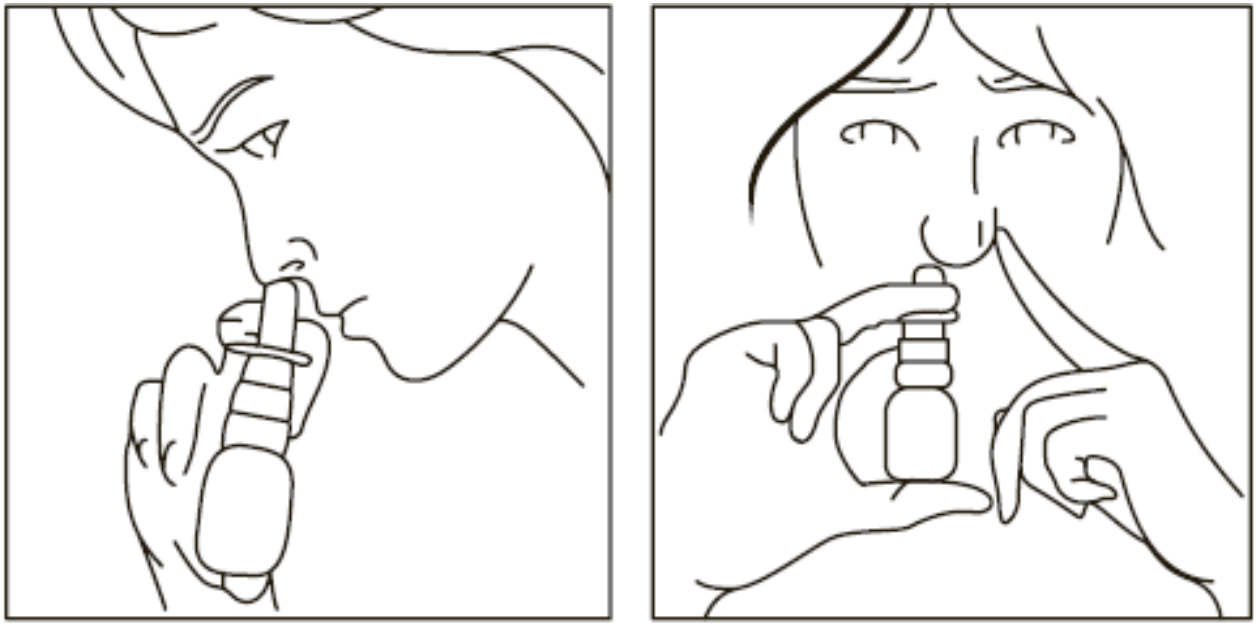
Table 15.4 Head position recommended in product labeling

Product	Device	Head position
Beconase (beclomethasone)	pMDI	Tilt your head forward slightly
Nasacort AQ (triamcinolone)	mMDP	Tip your head back a little and aim the spray toward the back of your nose
Nasacort HFA	pMDI	Tilt your head back slightly (side rather than septum)
FluMist (atten influenza virus)	Single dose sprayer	Head upright
Miacalcin (calcitonin) nasal solution	mMDP	Head upright
Synarel (naferlin)	mMDP	Tilt head forward during administration of the dose, then tilt it back to spread the dose
Atrovent nasal solution	mMDP	Tilt head forward, bottle upright and pointed back towards the outer side of the nose
Astelin nasal solution	mMDP	Tilt head forward to keep the medicine from going down throat
Imitrex nasal solution	Single dose spray	Head upright
Desmopressin acetate nasal solution	mMDP	Tilt head forward so that the mMDP can remain upright
Afrin nasal solution	Squeeze bottle	Head upright

pMDI = propelled metered dose inhaler; mMDP = mechanical metered dose pump.

Lying-head-back position





Head up-right

Figure 15.5 Head-forward position for administration of drugs from nasal metered dose pumps. (Reproduced with permission from Synarel packaging.)

- As questions?

1) What is the preferred nasal formulation?
2) What is the meaning of Nasal vaccines?
3) What about CNS delivery of drugs via nasal route? Can be or not.