Drug Delivery Systems

Nasal Drug Delivery

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Nasal Drug Delivery

- Intranasal drug delivery is a **convenient and accessible route** for rapid management of **localized nasal symptoms**, such as: allergic rhinitis, nasal congestion and nasal infections.

- Common intranasal drugs: **Antihistamines**, **corticosteroids**, sodium cromoglicate, sympathomimetics and **antiseptics/antibiotics**.

- Intranasal route is exploited for delivering drugs for:

i. **Local effect** of drug (e.g. Decongestants and antihistamines).
ii. **Systemic delivery** for the drug (e.g. Hormones as Desmopressin, analgesics and peptides).
iii. **CNS delivery** (e.g. Drugs for epilepsy and migraine).

Drug	Drug class	Use	Delivery system
Preparations for local effect			
Azelastine HCL	Antihistamine	Allergic rhinitis	Metered spray
Ephedrine HCL & Xylometazoline	Sympathomimetic	Nasal congestion	Nasal drops
Ipratropium bromide	Antimuscarinic	Rhinorrhea	Metered spray
Chlorhexidine and neomycin	Antibacterial	Elimination of staphylococci	Cream
Mupirocin	Antibacterial	MRSA elimination	Ointment
Preparations for systemic effect			
Desmopressin	Pituitary hormone	Diabetes insipidus & mild hemophilia	Metered spray

Drug	Drug class	Use	Delivery system
Glucagon	Polypeptide	Hypoglycemia	Unit basal powdered aerosol
Sumatriptan	5-HT1 agonist	Migraine	Unit dose spray
Nasal vaccines			
Influenza	Live attenuated virus	Vaccination	Prefilled-unit dose syringe

❑ Anatomy and physiology:

- The nasal cavity extends **120 – 140 mm** from the nostrils to the nasopharynx.
- Divided into **two cavities** by the nasal septum.
- Total surface area: ~ **160 cm^2** and total volume: **~ 15 ml.**

- **Parts of the nasal cavity:**

1. Nasal vestibule: (الدهليز الأنفي)

➢ First and narrowest part of the nasal cavity (Area 30 mm^2 per side).

➢ The lining changes from **skin at the entrance** to **stratified squamous epithelium** over the anterior **one-third of the nasal cavity**, contains **hairs that filter inhaled particles >10 µm.**

2. Turbinate region:

➢ Formed by convoluted **projections from the nasal septum.**

➢ Lined with **pseudostratified columnar epithelium**.

- Cell types present: **Mucus-secreting goblet cells**, **ciliated and non-ciliated epithelial cells**, and **basal cells.**

3. Cilia and microvilli:

- Apical surfaces of epithelial cells covered with **nonmotile microvilli** to **increase surface area.**

- Each ciliated cell has about **100 motile cilia.**

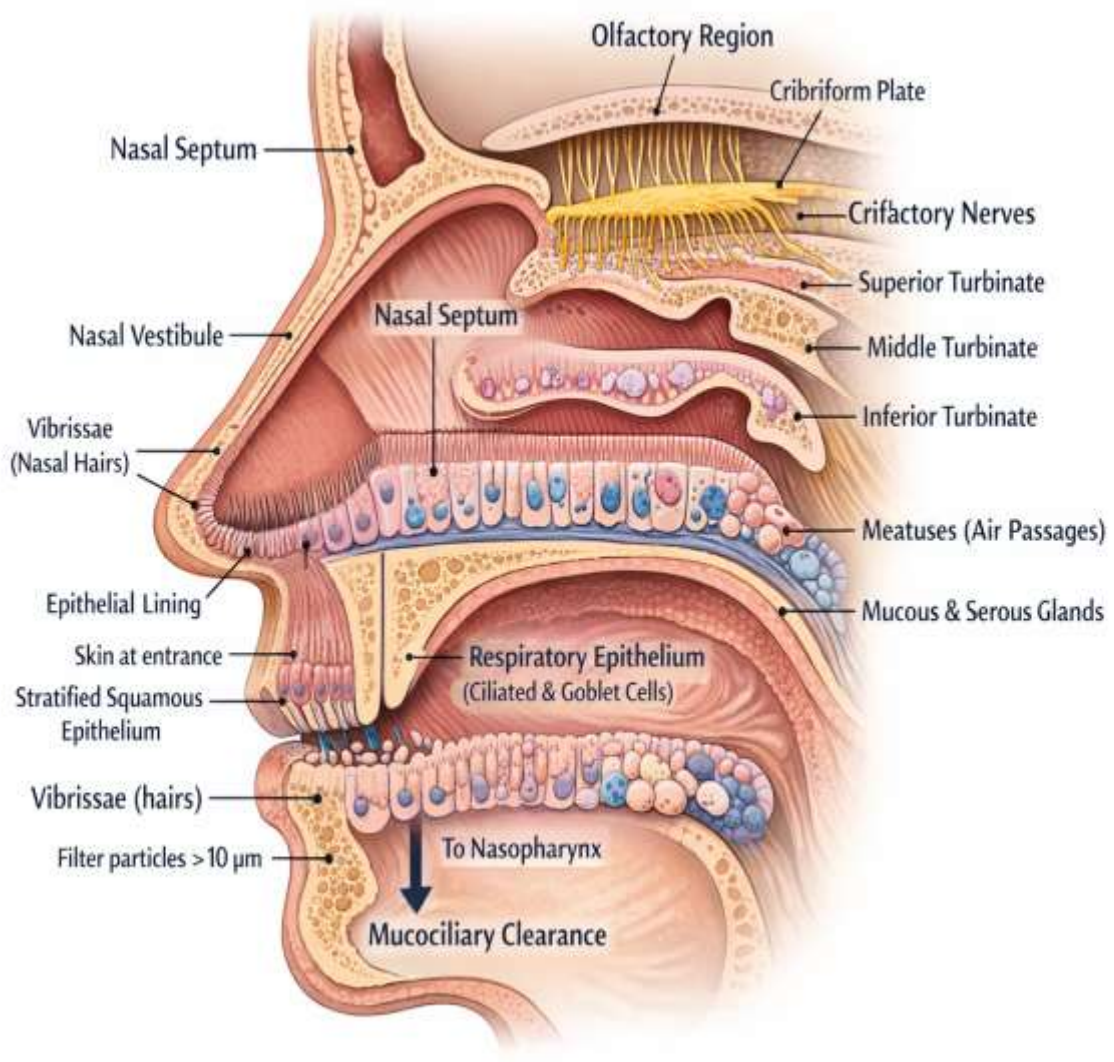
- **Cilia are responsible for mucus transport**.

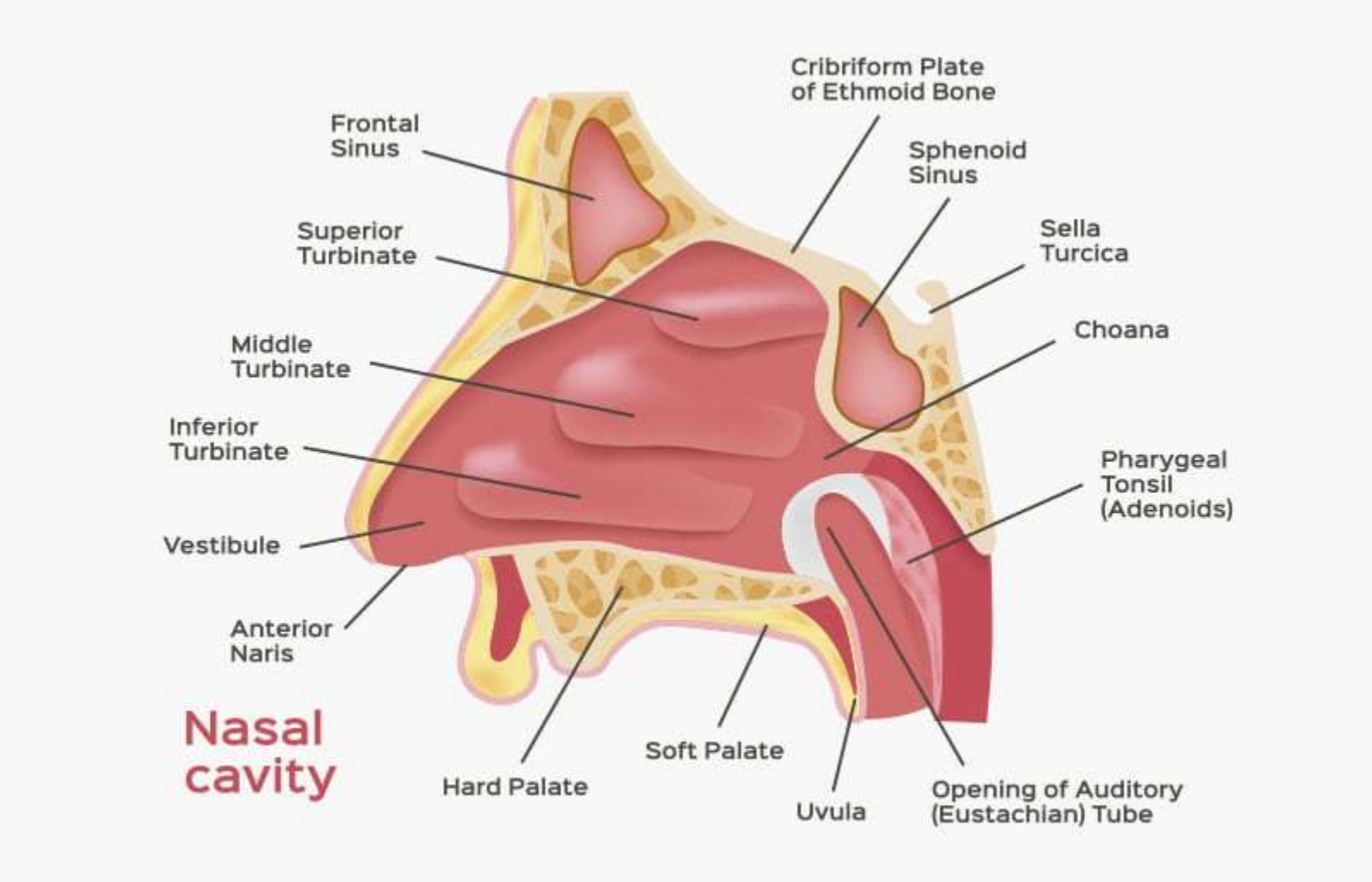
- Particles sized **5–10 µm** (dust, pollen, microorganisms, pollutants) can **deposit on the mucus layer.**

- Deposited material is either **swallowed or expectorated**.
- This process is known as mucociliary clearance **(clearance rate is 7mm/min).**

4. Olfactory region:

- Receives approximately **20% of inspired air**, **located at the top of the turbinates.**
- Lined with **non-ciliated pseudostratified columnar epithelium.**
- Contains 6–10 million **olfactory sensory neurons** → which pass **from the nasal cavity to the olfactory bulb of the brain.**





Structure of the nasal cavity

- **Olfactory Region and CNS Drug Delivery**

i. Location: **Upper nasal cavity** (olfactory region).

ii. Potential: Drugs administered in it could **bypass blood–brain barrier** (BBB) to be delivered **directly to the CNS.**

iii. Physiological link: Direct connection **between environment and brain**.

iv. Therapeutic applications: Potential for treating **Alzheimer's, brain tumors, epilepsy, pain, and sleep disorders.**

v. Current research: Increasing evidence from rodent and human studies supports its promise.

❑ **Drug delivery:**

A. 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.**

B. Systemic delivery:

- The rationale for using the nasal cavity for systemic delivery includes its accessibility, **avoidance of presystemic metabolism** and potential to provide a **rapid onset of action** for drugs with the appropriate physicochemical properties.

Intranasal drug delivery for systemic activity	
Advantages	**Disadvantages**
Large surface area for absorption (160 cm^2)	Limited to small delivery volumes (25 to 200 µL), therefore, potent drugs are required
Good blood supply and lymphatic system	Mucociliary clearance and/or barrier provided by mucus decrease absorption of some drugs
Avoids hepatic first-pass metabolism of oral route	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; absorption enhancers and/or large doses are required
Noninvasive, so minimal infection risk during application and low risk of disease transmission (unlike parenteral route)	
Easy to self-administer and adjust dose	

❑ Pathways for intranasal systemic drug delivery:

➢ To reach systemic circulation, drugs must be absorbed across the nasal epithelium.

1) Passive Diffusion Pathways:

i. Transcellular route:

✓ Primary pathway for **lipophilic drugs.**

✓ Drug diffuses **through epithelial cell membranes.**

ii. Paracellular route:

✓ Used by small **hydrophilic molecules.**

✓ Diffusion occurs **between epithelial cells via tight junctions.**

✓ Allow the passage of molecules with size **0.39 – 0.84 nm.**

2) Other absorptive mechanisms:

i. Endocytosis: Used by some **large hydrophilic molecules (>1 kDa).**

ii. Active transport:

- Drug resembles a natural substrate.
- Transported **via carrier proteins.**

- Factors Enhancing intranasal absorption:

i. Majority of drugs **absorbed via passive diffusion.**

ii. **Large surface area** of the nasal cavity.

iii. **Rich blood supply** → **maintains concentration gradient** → enhances absorption efficiency.

- **Barriers to intranasal drug systemic absorption:**

i. Mucus layer → Limits drug diffusion to the epithelial surface.
ii. Nasal epithelium → Acts as a physical and biochemical barrier.
iii. Mucociliary clearance → Removes drug-containing mucus.
iv. Enzymatic metabolism → Degrades drugs before absorption.

A. Mucociliary clearance:

- The **primary nasal absorption site** is the **respiratory epithelium of the nasal turbinates** where mucociliary clearance is dominant.
- In the anterior nasal cavity (**vestibular region**), drug **remains longer** in the cavity → But, lower absorption efficiency **(less vascularized).**
- In the turbinate region → **higher absorption potential** → However, **faster clearance** due to mucociliary activity.

- Rapidly absorbed drugs:

i. **Lipophilic** molecules.
ii. **Low molecular weight**.
iii. **Limited contact time still sufficient for complete absorption.**

- Slowly absorbed drugs:

i. **Suspensions requiring dissolution**.
ii. **Polar molecules with low permeability.**
iii. Absorption significantly limited by **mucociliary clearance**.

B. Barrier provided by mucus:

- Protective mucus layer shields the nasal mucosa from the external environment.
- **Two distinct layers** in the nasal cavity:

1. Gel layer:

➢ Thickness: ~ 1–10 µm.
➢ Acts as a **protective and trapping barrier**.

2. Sol (periciliary) layer:

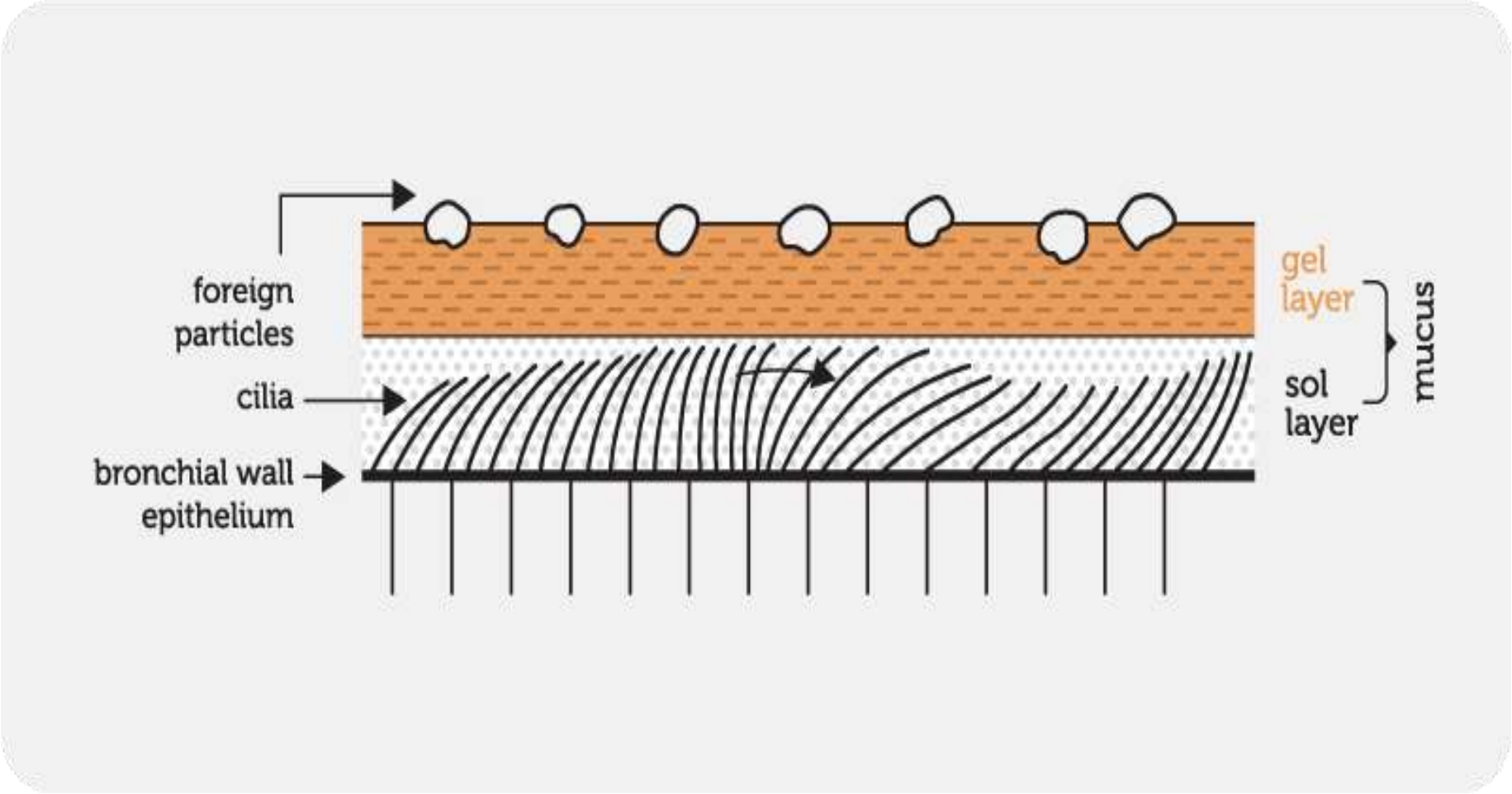
- **Watery layer** surrounding the cilia.
- Depth: ~ 7 µm.
- Allows **effective ciliary movement.**

- Mucus at the epithelial surface acts as an additional diffusion barrier to drug delivery.

- Factors influencing diffusion through mucus:

i. Drug molecular size.
ii. Effective **mesh size of the mucous gel** **(mucin network)** (i.e. The average **distance between adjacent mucin fibers in the gel).**
iii. Drug–mucus interactions.

- **Small, uncharged molecules diffuse relatively easily** through mucus.
- **Larger, cationic molecules** diffusion significantly **hindered** by the mucous barrier.



Structure of mucous layer

C. Enzymatic activity:

1. Phase I metabolism: **Monooxygenases**, **carboxyl esterases**, epoxide hydrolases and **CYP-450 isoenzymes.**

2. Phase II (Conjugative) metabolism: **UDP-glucuronyl transferase** and **glutathione S-transferase.**

3. Proteolytic Enzymes: **Proteases and aminopeptidases** → **Limit absorption of peptide drugs.**

- Drug metabolism may **occur in the nasal lumen** during passage across the nasal epithelium.

- Factors affecting drug metabolism:

i. **Amount of drug** applied to the nasal surface (At **low doses** → enzymes are not saturated → higher fraction metabolized).

ii. **Chemical nature** of the drug (Lipophilic drugs → Cross membrane rapidly → Less exposed to luminal enzymes).

iii. **Rate of drug removal** from the nasal cavity.
iv. **Rate of absorption** across the nasal mucosa.

D. Efflux transporter and nasal drug absorption:

- Absorption of some drugs is limited by efflux transporters.
- These transporters **actively reduce drug uptake** across the nasal epithelium.
- **P-Glycoprotein (P-gp)** is a member of the ATP-binding cassette (ABC) transporter superfamily, also known as **multidrug resistance protein 1 (MDR1) or ABCB1**.
- Expressed in **nasal respiratory mucosa** and gastrointestinal tract (similar barrier to oral drugs).
- Most substrates: **Hydrophobic, amphiphilic compounds, certain peptides, and molecular weight › 400 Da.**

- Transport Characteristics:

i. Energy-dependent **(ATP-driven).**
ii. Operates **against a concentration gradient.**
iii. Saturable.
iv. Competitively **inhibited** by other substrates **(P-gp inhibitors).**

- Modulation of P-gp Activity:

i. Coadministration of P-gp inhibitors can enhance absorption.
ii. Examples: **Rifampicin and verapamil**.

- **P-gp** in the **olfactory epithelium at a higher concentration** than is found in the **respiratory epithelium**.

i. Reduce drug transport.
ii. Limit drug entry into the brain.

❑ **Physicochemical properties of drugs affecting intranasal systemic delivery:**

- For absorption, a drug **must generally be in solution** (molecularly dispersed).

- The **intranasal administration volume is limited (25–200 µL),** which creates challenges for drugs with **low aqueous solubility and drugs requiring high doses.**

- These limitations can be addressed by formulating drugs as **suspensions** or powders with **micrometer-sized particles**.

- In such formulations, **the drug must dissolve in nasal cavity fluid** before absorption.

- Evidence suggests that **nanoparticles** may be:

i. Transported into the **systemic circulation without dissolving.**
ii. Absorbed via mechanisms involving **nasal-associated lymphoid tissue (NALT).**

A. Solubility:

- Strategies to increase drug solubility include:

i. Selection of an **alternative salt form.**
ii. **Modification of the molecular structure**, including use of a **prodrug**.
iii. Incorporation of suitable excipients (e.g., **cosolvents**) in the formulation.

- **Prodrugs** are commonly developed to:

i. **Increase lipophilicity**.
ii. **Enhance membrane permeability and absorption**.
iii. Increase **aqueous solubility** of the parent drug.
iv. Allow a clinically **effective dose to be dissolved in < 150 µL of formulation.**

- **Salt selection is largely an empirical process** because the effect of a **specific counterion on solubility is difficult to predict reliably.**

- Despite this uncertainty, there are documented cases where salt selection has successfully improved drug solubility.

- However, a change in **salt form can result in irritancy to the nasal mucosa** and this has to be considered when an **appropriate counterion** is being chosen.

B. Lipophilicity/hydrophilicity and molecular size:

- **Lipophilic drugs (e.g., propranolol, progesterone, fentanyl):**

i. Are **rapidly absorbed** from the nasal cavity once in solution.
ii. Use the **transcellular route**.
iii. Exhibit **nasal bioavailability ≈ intravenous administration (≈100%).**

- **Hydrophilic (polar) drugs:**

i. Are absorbed via the **paracellular route.**
ii. Pass between epithelial cells **through tight junctions.**
iii. Rate and extent of **absorption** is **inversely proportional** to **molecular weight.**

- Paracellular route:

i. Much **smaller surface area.**

ii. Lower absorption capacity.

- Transcellular route:

i. Larger surface area.

ii. More **efficient absorption.**

C. Degree of ionization:

- Effect of pH on weak acids and bases:

i. Nasal cavity **pH influences the degree of drug ionization**.

ii. pH at the **nasal mucosal surface ≈ 7.4.**

iii. pH of **nasal mucus ≈ 5.5–6.5.**

- The pH of the formulation can modify local nasal pH.
- Effects are **more pronounced when buffered vehicles are used.**

- Un-ionized drug form:

i. **Higher oil–water partition coefficient.**
ii. **Better absorption across nasal epithelium.**
iii. Explained by the pH-partition hypothesis.

- Ionized drug form:

i. Still exhibits **some permeation.**
ii. Extent of absorption may depend on the counterion **(via carrier-mediated, paracellular, ion-pair formation or high conc. gradient).**

❑ Formulation factors affecting intranasal systemic delivery:

- General formulation principles are similar for systemic and local nasal drug delivery.

- **Additional strategies** may be **required to enhance absorption** across the nasal epithelium.

- Factors limiting nasal drug bioavailability:

i. **Low aqueous solubility.**
ii. **Rapid enzymatic degradation** within the nasal cavity.
iii. **Short residence time** at the absorptive epithelium due to **mucociliary clearance** in the turbinates and poor permeation across the respiratory epithelium.

A. Increasing aqueous solubility:

- Drugs must generally be in solution to be absorbed.
- Using of mixed solvent systems or **co-solvents in the formulation** may improve drug solubility.
- Co-solvents used in nasal delivery: **Glycerol, Ethanol, Propylene glycol, and Polyethylene glycol (PEG).**
- Co-solvents must be **non-irritating** to the nasal mucosa.
- **High concentrations of ethanol** are likely to be **poorly tolerated.**

B. pH of the formulation:

- Many drugs are weak acids or bases.
- Absorption **depends on drug pKa and pH** at the absorption site.
- Formulation pH is primarily determined by drug stability.
- Within stability limits, a **pH that favors the un-ionized form is expected to enhance absorption.**
- Formulations must be **non-irritant** to the nasal mucosa.
- A pH close to nasal cavity pH (5.0–6.5) is generally preferred, however, studies show the **nasal mucosa can tolerate a wide pH range (3–10).**

C. Use of enzyme inhibitors:

- **Proteolytic enzyme inhibitors** could **prevent the hydrolysis of peptide and protein drugs in the nasal cavity**, improving their stability at the absorption site (e.g. **Camostat mesylate is an inhibitor for aminopeptidase and trypsin enzymes**).

- Proteolytic enzyme inhibitors do not improve the ability of peptide drugs to cross the epithelium of the nasal cavity → **NOT increase nasal bioavailability**, as clearance mechanisms continue to operate to remove the drug from the absorption site.

D. Increasing nasal residence time:

- If a **drug lacks ideal properties for rapid absorption** → the fraction reaching systemic circulation **depends on residence time** in the nasal turbinates.

- Use of **mucoadhesive polymers** to prolong contact with absorptive mucosa.

- Examples of mucoadhesive polymers: **Cellulose derivatives, polyacrylates, starch and chitosan.**

- Mucoadhesives can enhance drug absorption via three mechanisms:

1. **Prolonging residence time:**

✓ **Optimal hydration extends polymer chains.**

✓ **Chains interact with nasal tissue, resisting mucociliary clearance.**

✓ Increases formulation retention in the nasal cavity.

2. **Protecting the drug:**

✓ Act as **carriers**.

✓ **Reduce contact between drug and nasal enzymes.**

✓ Protects drug from potential degradation.

3. **Modulating epithelial permeability:**

✓ Some polymers **affect tight junctions** between epithelial cells.

✓ **Hydration of polymer causes temporary dehydration of cells**.

✓ Opens tight junctions, **increasing paracellular drug absorption.**

- Effect of **prolonged exposure** of mucoadhesive polymers:

i. **Continuous mucus production** leads to **over-hydration of the polymer.**
ii. Excess hydration **reduces mucoadhesive strength.**
iii. **Normal mucociliary clearance resumes.**
iv. Polymer is eventually **cleared from the nasal cavity.**

- Polymers are **not mucoadhesive when dry (powder form)** → allow easy **metered-dose administration** → become mucoadhesive upon contact with nasal mucus (absorb water).

➢ Advantages of powder forms over liquid formulations:

i. Can **deliver larger amounts of drug.**
ii. **No preservatives needed** (do not support microbial growth).
iii. **Better stability** → no need for reduced-temperature storage.

- Applications: Suitable for small hydrophobic drugs, peptides, and vaccines.

- Disadvantages / limitations:

i. Possible nasal mucosa **irritation**.
ii. Potential **gritty texture.**
iii. Aerodynamic **particle size affects deposition site** in nasal cavity.

E. Enhancing the permeability of the nasal epithelium:

- Use of **permeation enhancers can increase absorption** of small and large **hydrophilic drugs** by **modifying the structure of the nasal epithelium.**

- Alterations to epithelial barrier function **must be short-term and reversible**.

- Ideal characteristics of a nasal permeation enhancer:

i. Rapidly acting with **transient and reversible effects** on the nasal epithelium.
ii. Not absorbed systemically.

iii. **Non-toxic, non-irritant, and non-allergenic.**
iv. **Compatible with the drug** and other formulation excipients.
v. **Safe for long-term use** (as appropriate for the treated condition).

- Examples: **Surfactants** (e.g. **bile salts**), **cationic polymers** (e.g. **chitosan**, cationized gelatin), **cell-penetrating peptides** (e.g. **Octa-arginine**), and **cyclodextrin**.

❑ **Patient factors affecting intranasal systemic delivery:**

i. **Patient adherence** : If a patient does not use a medication appropriately, then it cannot be expected to be effective.

ii. **Disease**: A number of **nasal diseases** affect the absorption of drugs into the systemic circulation, either by **altering nasal mucociliary clearance** (e.g. the **common cold**) or by **affecting the permeability** of the nasal epithelium (e.g. **allergic rhinitis**).

❑ **Nasal vaccines:**

- **Intramuscular (needle-based) vaccination:**

i. **Induce serum antibodies (IgG).**
ii. **IgG transudes to the lungs → protects lower respiratory tract.**
iii. **Reduces severe influenza complications.**

- **Intranasal vaccination:**

i. Induce **local IgA responses** in the upper respiratory tract.
ii. Also **stimulate systemic IgG responses**.
iii. IgA neutralizes virus immediately after inhalation → **protects against early symptoms.**
iv. Secretory **IgA is more cross-reactive than IgG → can protect against multiple virus strains.**

- Benefits of nasal vaccination vs. needle-based delivery:

i. **Reduced risk of needle-stick injuries**.
ii. **Lower risk of infection** from needle reuse.
iii. Improved **patient adherence**, especially in those with needle phobia.
iv. **Less dependence on trained healthcare** professionals for administration.
v. Potentially **reduced cold-chain requirements** if vaccines are formulated as **dry powders**.

❑ **CNS delivery:**

- The BBB **restricts** the entry of potentially **harmful substances** into the brain but also **limits the access of potentially useful drugs.**
- Drugs delivered intranasally that enter the systemic circulation would have to cross the BBB to enter the CNS.
- However, there is a route from the **olfactory region** of the nasal cavity to the brain that **avoids the BBB** and which can be exploited to deliver drugs directly to the brain.

- The **olfactory mucosa** is composed of **olfactory epithelium and underlying lamina propria.**

- **Routes of molecular transport:**

i. Intracellular / Axonal pathway:

➢ Substances taken up by olfactory sensory neurons (OSNs) **(Transported along the axon to the olfactory bulb) via:**

a) **Adsorptive endocytosis** (via electrostatic interaction).
b) **Receptor-mediated endocytosis.**
c) Nonspecific **fluid-phase endocytosis** (pinocytosis).

ii. Transcellular / Paracellular pathway **via other epithelial cells:**

➢ Movement occurs by **passive diffusion (transcellular or paracellular)** to reach the lamina propria.

- **Tight junctions** normally **restrict passage**, but **epithelial cell turnover can loosen junctions**, facilitating transport of larger molecules.

iii. The **trigeminal nerve**, which **innervates the respiratory epithelium of the nasal cavity,** also feeds into various areas of the brain and could potentially be exploited for nose-to-brain drug delivery **(Mainly extracellular).**

- Mechanisms of **entry from lamina propria into CNS** (extracellularly):

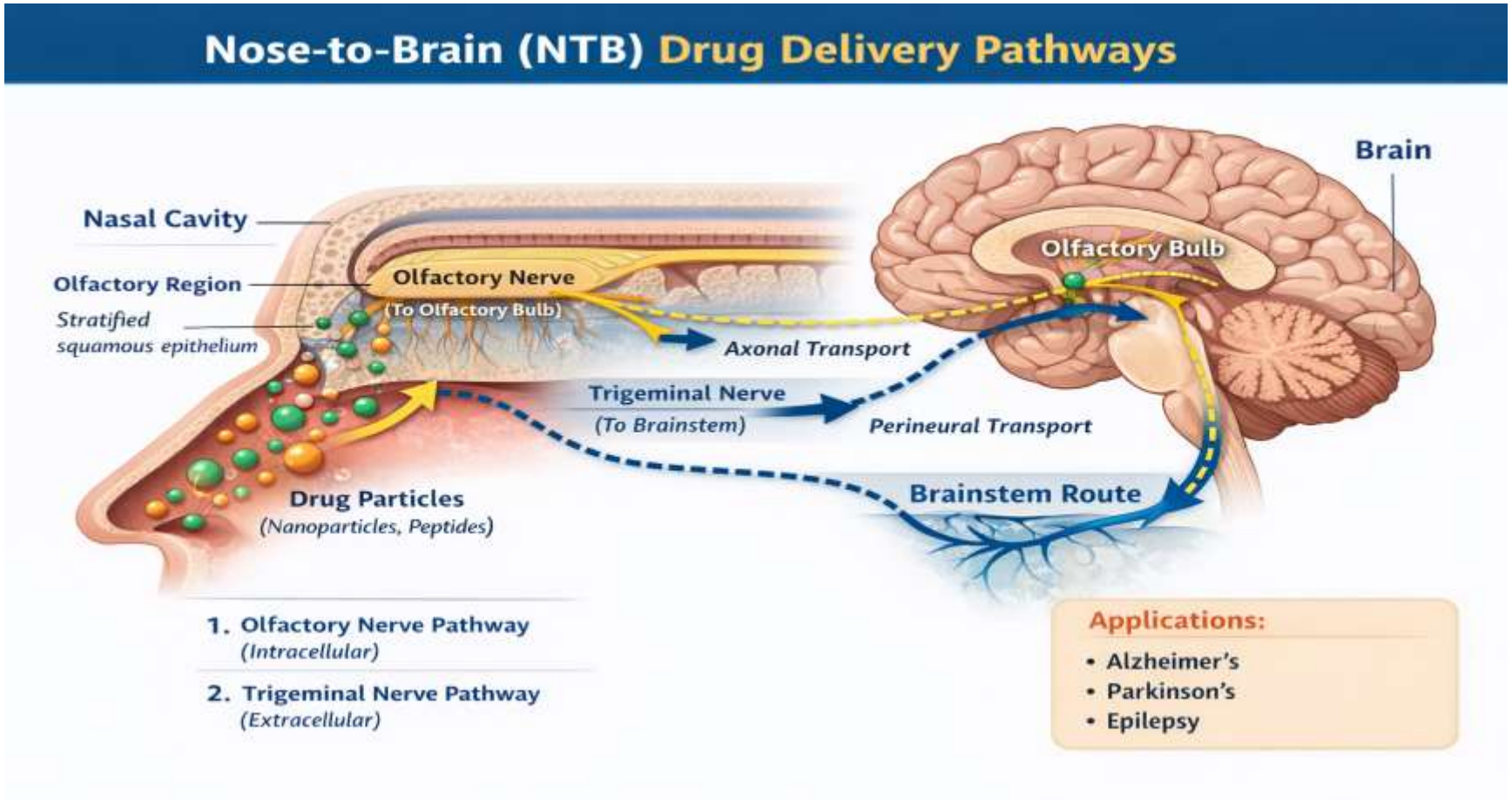
i. **Diffusion (via concentration gradient).**
ii. **Bulk flow (Driven by pressure gradient).**
iii. **Perivascular pump** along perineural space surrounding olfactory nerve bundles.

✓ Passage from lamina propria → through the **cribriform plate** into the **CSF or olfactory bulb.**

- **Notes:**

➢ **Intracellular (axonal) transport** via OSNs is likely **too slow.**

➢ **Extracellular perineural pathway** is considered the primary route for **rapid CNS delivery.**



Feature	Olfactory Pathway	Trigeminal Pathway
Anatomical Location	Olfactory region (upper posterior nasal cavity)	Respiratory region (throughout nasal cavity)
Nerve Involved	Olfactory nerve (Cranial Nerve I)	Trigeminal nerve (Cranial Nerve V)
Primary Brain Target	Olfactory bulb → Forebrain	Brainstem → Spinal cord → Other CNS regions
Type of Transport	Mainly intracellular (axonal transport) + extracellular	Mainly extracellular (perineural transport)
Transport Speed	Slower (hours to days for axonal transport)	Faster (minutes to hours via perineural diffusion)
Drug Deposition Requirement	Requires deposition in upper nasal cavity	Can occur from wider nasal regions
Surface Area	Small (~5–10% of nasal cavity)	Larger (respiratory epithelium dominant)
Role in NTB Delivery	Direct targeting of forebrain	Broader CNS distribution, especially brainstem
Importance for CNS Diseases	Alzheimer’s, Parkinson’s	Epilepsy, pain modulation, brainstem disorders

❑ **Nasal delivery systems:**

- Common nasal dosage formulations:

i. **Ointments or creams.**
ii. **Liquids**: solution or suspension.
iii. **Powdered** solids.

A. Multidose liquid forms:

i. Risk of **"suck back"** → **part of the dose returns to the device.**
ii. Require **antimicrobial preservatives** to prevent microbial growth.
iii. Some preservatives can **irritate nasal mucosa** and damage cilia, compromising mucociliary clearance, especially with long-term use.

- Strategies **to minimize preservative-related effects**:

i. **Alternate nostril administration** for long-term daily use.
ii. Use **unit-dose systems** → avoid preservatives.

- Trends in delivery systems:

i. Shift towards accurate **metered-dose devices.**

ii. Moving **away from nasal drops** → require skill and mobility to be applied.

iii. **Smaller volumes** (<100 µL) **persist longer than larger volumes**, which may drip from the nostril.

B. Powdered solids:

- **Remain** in the nasal cavity **longer than liquids.**
- **Preliminary hydration delays** maximal **mucociliary clearance.**
- **Prolongs systemic drug absorption** and duration of action for locally acting drugs.

C. Creams and ointments:

i. Also **prolong retention** in the nasal cavity.

ii. **Limit rapid fluid flow to throat/mouth** → reduces **unpleasant taste**, coughing, and gagging.

- Particle size considerations:

i. **< 10 µm** → May **move beyond turbinates toward lungs.**
ii. **> 50 µm** → **Cleared more rapidly** by mucociliary action or nose blowing.


Thank you