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Nasal Drug Delivery System: Formulation Strategies and Design Challenges

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Abstract: Nasal drug delivery systems represent a promising non-invasive strategy for enhancing systemic bioavailability, particularly for medications with poor oral absorption, by bypassing first-pass hepatic metabolism and enabling rapid onset through the highly vascularized nasal mucosa with surface area approximately 150 cm² and volume 15 ml. This route is especially valuable for central nervous system disorders affecting over a billion people globally, as it facilitates blood-brain barrier crossing via olfactory pathways, while offering advantages like lower doses, reduced side effects, improved peptide/protein absorption with enhancers, and high patient compliance via self-administration. Absorption occurs primarily via paracellular pathway for hydrophilic drugs or transcellular pathway for lipophilic drugs, with barriers mitigated by ideal drug traits like low dose under 25 mg, solubility, and stability. Formulation strategies employ excipients such as chitosan for permeation, HPMC for viscosity, preservatives like benzalkonium chloride, dosage forms including drops, metered sprays like oxymetazoline or fluticasone for decongestion/rhinitis, gels for retention, powders for stability, and advanced carriers like liposomes, microspheres, nanoparticles to prolong residence, sustain release, and boost efficacy. Despite drawbacks like irritation and smaller absorption surface versus gastrointestinal tract, ongoing innovations in muco-adhesives and devices position nasal delivery as a viable alternative to injections, particularly for central nervous system targeting and local therapies.

Keywords: *Nasal Drug Delivery, Systemic Bioavailability, BBB Crossing, Nasal Sprays, Permeation Enhancers, Mucoadhesive Agents.*

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I. INTRODUCTION

Many medications now have greater systemic bioavailability when administered nasally as opposed to orally. (1) Compared to other traditional medication delivery methods, the nasal route is thought to be a potential systemic administration option. By avoiding first-pass hepatic metabolism, nasal administration of the medication has fewer side effects and a quicker onset of action at lower doses. (2) Our knowledge of the underlying causes and management of illnesses of the central nervous system has significantly improved during the last 20 years. (3) Approximately 98–100% of therapeutic agents are unable to cross the blood–brain barrier (BBB) efficiently, which highlights the importance of alternative routes such as nasal delivery for targeting the central nervous system. According to the World Health Organization, neurological disorders affect more than 1 billion people globally. (4,5)

For topical nasal disorders like decongestion and rhinitis, intranasal medication administration has long been investigated. The ayurvedic system of Indian medicine has acknowledged nasal therapy, also known as Nasaya karma, as a kind of treatment. With a highly vascularized epithelium and porous endothelium membrane that facilitates quick drug absorption, nasal medication delivery is dependable and conveniently accessible. (6,7)

For medications that have poor oral bioavailability and are active at low doses, nasal drug delivery is a helpful delivery strategy. Due to their instability in the gastrointestinal tract, low absorption characteristics, and quick and extensive biotransformation, these chemicals are important candidates that are typically supplied by injection and barely absorbed after oral administration. For the administration of peptides and protein medications in particular, nasal delivery is a viable alternative method. There are now two kinds of nasally administered medications available. The first one includes hydrophobic and low molecular weight medications, such as decongestants, topical steroids, antibiotics, and other items, that are used to treat sinuses and nasal mucosa. A few medications that have enough nasal absorption to exhibit systemic effects fall into the second class. (8)

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II. ANATOMY AND PHYSIOLOGY OF NASAL CAVITY

The nasal cavity's path from the nasal vestibule to the nasopharynx is between 12 and 14 cm deep. An adult human's nasal cavity has a total size of roughly 150 cm2 and a total volume of approximately 15 ml. [9,10] The middle septum divides the nasal cavity into two symmetrical halves, each of which extends posteriorly to the nasopharynx and opens at the face through the nostrils. The four regions that make up both symmetrical halves (the nasal vestibule, atrium, respiratory region, and olfactory region) are differentiated based on their anatomical and histological features. The nasal vestibule, inferior turbinate, middle turbinate, superior turbinate, olfactory area, frontal sinus, sphenoidal sinus, and cribriform plate of ethmoid bone are the several regions that make up each of the two nasal cavities. The nasal associated lymphoid tissue (NALT), which is primarily located in the nasopharynx, is another component of the nasal cavity. [11] Breathing and scent are the nasal cavity's primary purposes. But once it filters, warms, and humidifies the air before it reaches the lower respiratory tract, it also plays a significant protective role. [12] The mucous membrane that covers the nasal cavity can be separated into two zones: non-olfactory and olfactory epithelium. The non-olfactory area contains the nasal vestibule, which is covered in stratified skin-like squamous epithelial cells, while the respiratory region has the typical airway epithelium covered with many microvilli, which results in a large surface area available for drug absorption and transport. [13,14]

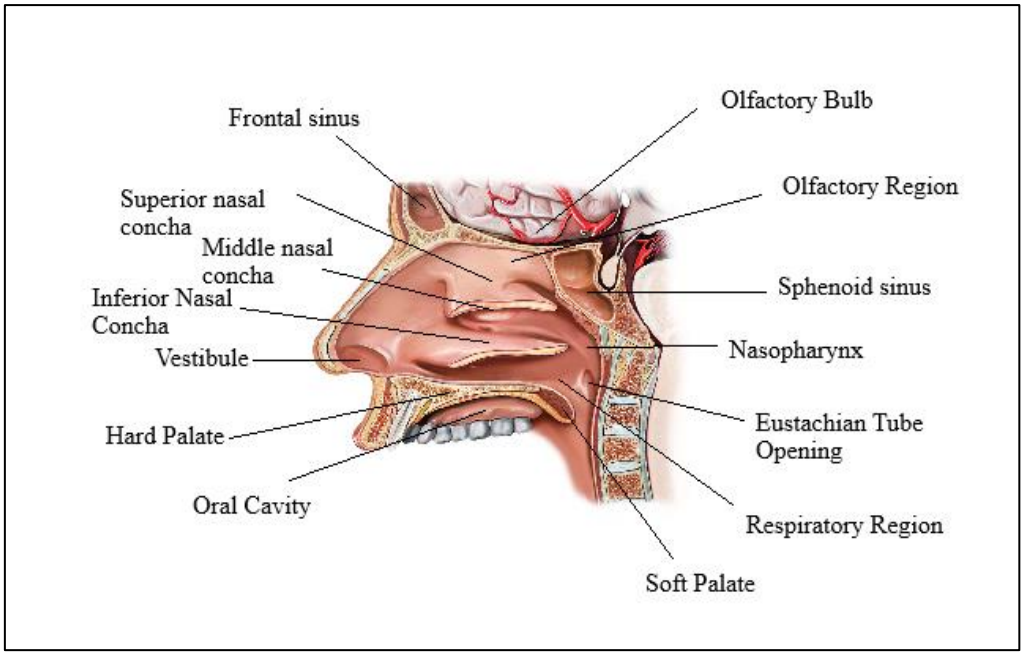

Fig 1 Anatomy of Nasal Cavity

➢ *Nasal Vestibule:*

The most anterior portion of the nasal cavity, the nasal vestibule is situated just inside the nostrils and takes up around 0.6 cm2. Nasal hairs that filter inhaled particles are located in this area. This nasal region is histologically covered by a stratified, keratinized squamous epithelium with sebaceous glands. [15]

➢ *Atrium:*

The area between the respiratory region and the nasal vestibule is known as the atrium. Pseudostratified columnar cells with microvilli make up the posterior region, whereas overlaid scaly epithelium makes up the anterior section. [16]

➢ *Respiratory Region:*

The greatest portion of the nasal cavity is the respiratory area, commonly referred to as the Conca. It is made up by upper, middle, and lower vortexes that protrude from the side wall. The nasal respiratory lining, which is thought to be the most crucial area for systemic medication distribution, is made up of the epithelium, basal membrane, and suitable lamina propria. The nasal respiratory epithelium is composed of pseudostratified columnary epithelial cells, goblet cells, basal cells, mucous membrane glands, and serous cocoecone. [17,18]

➢ *Olfactory Region:*

The olfactory area is located at the roof of the nasal cavity and extends a short distance along the lateral wall and septum. The only area of the central nervous system that is directly exposed to the outside world is its neuro-epithelium. The olfactory epithelium is pseudostratified, just like the respiratory epithelium, but it has specific olfactory receptor cells that are crucial for scent perception. [19]

➢ *Blood Flow to the Nasal Cavity:*

The nasal cavity's vasculature receives an abundance of blood to perform essential tasks like heating and humidification, smell, mucociliary clearance, and immunological processes. Rapid fluid and dissolved excipient exchange between blood vessels and nasal tissue is made simple by the nature of the nasal vascular bed. According to reports, the nasal mucosa's capillary flow is 0.5 ml/g/min. A branch of the maxillary artery is the

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sphenopalatine artery. An ophthalmic artery branch is the anterior ethmoidal artery. Facial artery branches that supply the nasal cavity's vestibule. [20]

➢ *Advantages of Nasal Delivery System*

- A quick commencement of action is possible with nasal medication administration.
- This approach improves patient comfort because it is non-invasive and simple to use.
- When medications are administered by the nose, they can avoid the blood-brain barrier.
- Nasal medication administration prevents drug breakdown in the gastrointestinal tract.
- Hepatic first-pass metabolism is eliminated by nasal medication administration.
- For tiny pharmacological compounds, the nasal route offers good absorption.
- The penetration enhancers can improve the bioavailability of big medicinal molecules.
- Many times, medications that are inappropriate for oral administration can be administered through the nose.
- Reduced systemic side effects and lower required doses result from improved
- bioavailability.
- Patient compliance is improved by the nasal route's convenience and ease of self-administration. [21,22,23]

➢ *Disadvantages of Nasal Delivery System*

- Compared to the gastrointestinal tract, the nasal cavity has a smaller absorption surface.
- The oral delivery technique may cause irritation.
- Local side effects and permanent harm to the nasal mucosa's eyelashes may result from the material and ingredient used to the dosage form.
- If the dosage form is administered incorrectly, it may be mechanically lost in other areas of the airways, such as the lungs.
- At high concentrations, certain surfactants utilized as chemical enhancers have the ability to rupture and even dissolve the membrane.
- The histopathological toxicity of absorption enhancers used to increase the nasal medication delivery route is still unknown.
- Compared to GIT, the absorption surface is smaller.
- The medication cannot be stopped once it has been administered.
- Irritation of the nose.
- The nasal cavity's transmission range is restricted to 25–200 µL(Microliters). [24,25,26,26]

➢ *Ideal Features of Nasal Drug Candidates*

The following qualities should be present in a perfect nasal medication candidate:

- The formulation should be administered in a volume of 25 to 150 ml per nostril with the appropriate aqueous solubility to deliver the required dose.
- Sufficient nasal absorption capabilities.
- The medication does not cause nasal discomfort.
- A suitable clinical rationale for nasal dose forms, such as quick action.
- Low dosage, often around 25 mg.
- There are no harmful nasal metabolites.
- The medication has no objectionable Odor.
- Sufficient stability features. [28,29]

III. MECHANISM OF NASAL DRUG ABSORPTION

The first step in absorption is for the medications that are taken in from the nasal cavity to pass through the layer. Large, charged medications have a harder time getting through this barrier than small, unaltered drugs. Mucin, the main protein in mucus, has a propensity to attach to solutes and prevent diffusion. Furthermore, environmental changes (such as variations in pH, temperature, etc.) may result in structural alterations in the mucus layer. [30]

➢ *Paracellular Pathway:*

The first mechanism is a sluggish, passive water route of transport, commonly referred to as the paracellular pathway. The molecular weight of water-soluble compounds and intranasal absorption have an inverse log-log association. Drugs with molecular weights larger than 1000 Daltons exhibit low bioavailability. [31]

➢ *Transcellular Pathway:*

It is also referred to as the transcellular process and involves transfer via a lipoidal pathway. It is in charge of carrying lipophilic medications whose rate is influenced by their lipophilicity. Additionally, drugs can pass across cell membranes through tight junction opening or active transport via carrier-mediated mechanisms. [32] For example, chitosan, a naturally occurring biopolymer derived from shellfish, facilitates medication delivery by opening tight junctions between epithelial cells. [33]

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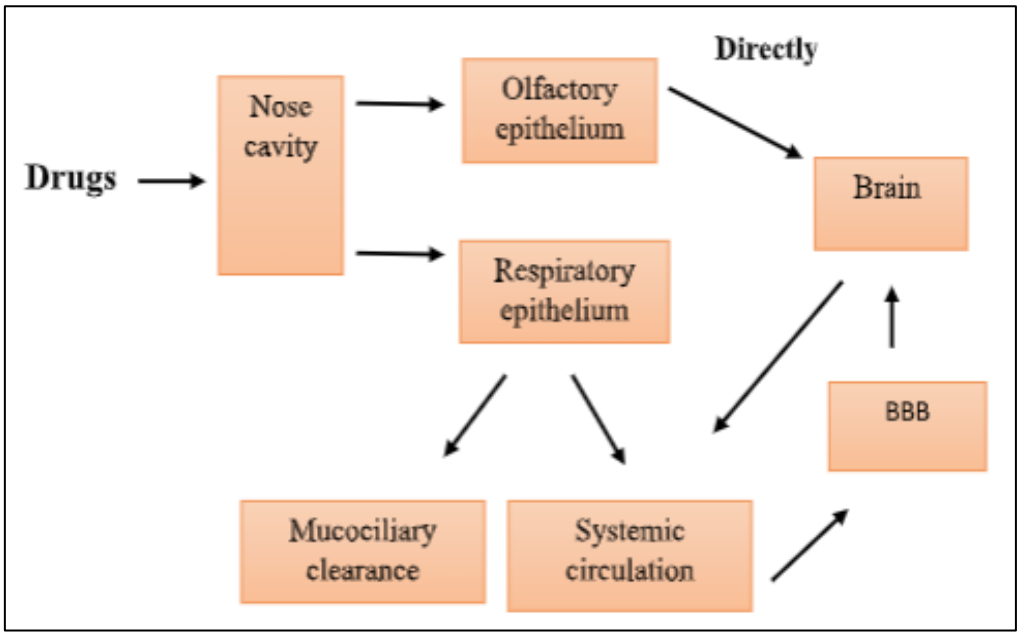

Fig 2 Nose to Brain Drug Delivery Pathway

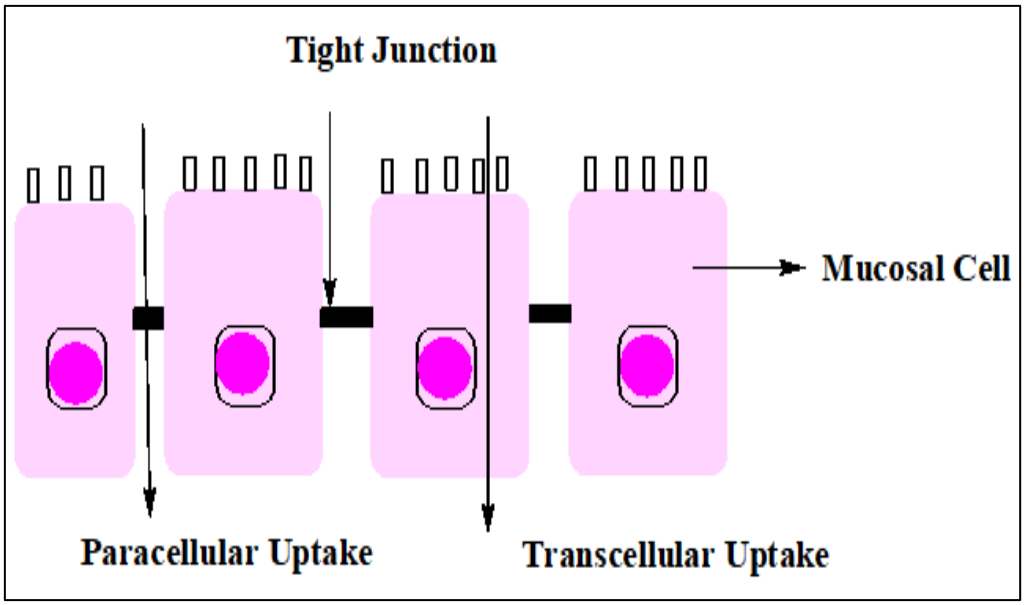

Fig 3 Mechanism of Nasal Absorption

IV. BARRIERS TO NASAL ABSORPTION

➢ *Low Bioavailability:*

Compared to polar medications, lipophilic medications are typically better absorbed from the nasal cavity. Little membrane permeability is the most important issue limiting the nasal absorption of polar medicines, particularly big molecular weight polar pharmaceuticals like proteins and peptides. Polar medications with molecular weights under 1000 Daltons typically use the paracellular pathway to cross the membrane. It has been demonstrated that larger proteins and peptides can cross the nasal membrane through endocytotic transport, albeit only in trace amounts. [34]

➢ *Low Membrane Transport:*

Because of the mucociliary clearance mechanism, the given formulation is quickly removed from the nasal cavity. This is particularly true for medications that are difficult to absorb via the nasal membrane.

➢ *Enzymatic Degradation:*

The potential of an enzymatic breakdown of the molecule either within the nasal cavity lumen or during passage across the epithelial barrier by exopeptidase and endopeptidase is associated with low transport, particularly of peptides and proteins across the nasal membrane. [35]

➢ *Factors Affecting Nasal Drug Absorption [36]*

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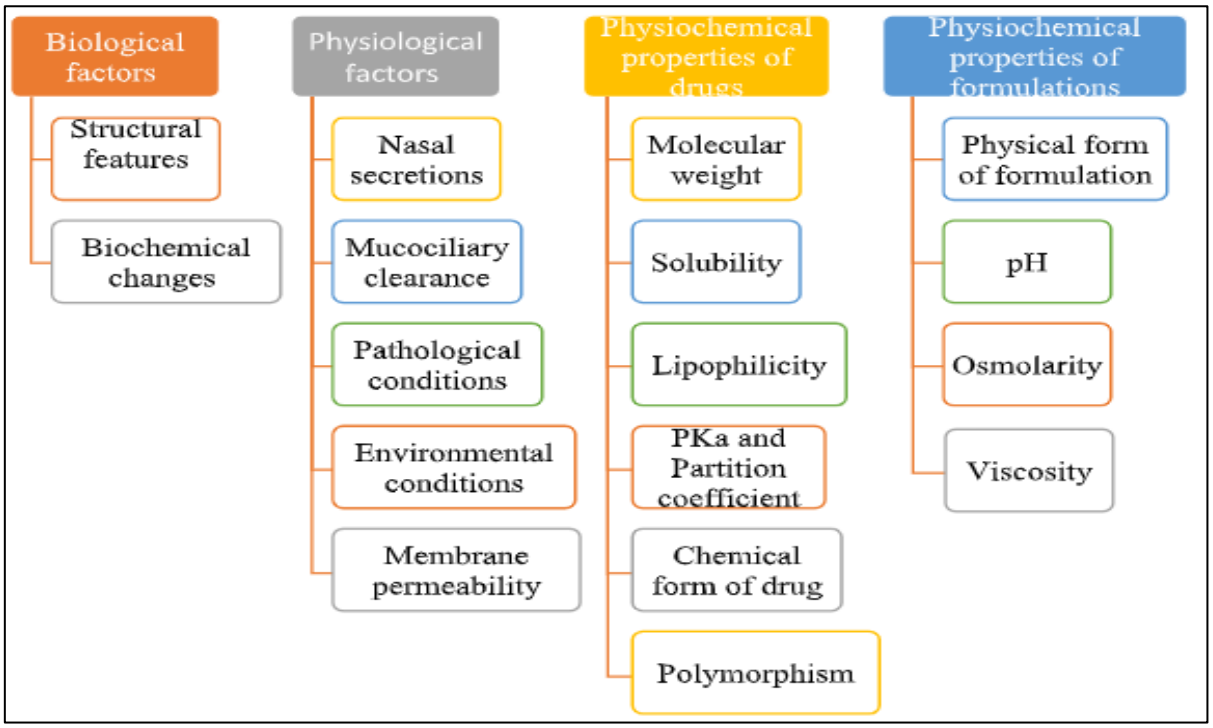

Fig 4 Factors Affecting Nasal Absorption

➢ *Formulation Strategies*

Formulation strategies enhance nasal drug delivery through sprays, gels and powders by employing excipients such as buffers alongside advanced nanocarriers and delivery devices.

- *Excipients Used in Nasal Formulations*

Table 1 Excipients Used in Nasal Formulations [37,38,39]

Category	Description	Function	Examples
Permeation Enhancers	To promote drug absorption, permeation enhancers temporarily alter the nasal epithelium.	Boost the nasal mucosa permeability.	Chitosan, Cyclodextrins, phospholipids.
Viscosity Enhancers	Viscosity enhancers assist the formulation stay in the nasal cavity longer and improve drug absorption by thickening it.	Increase the formulation's retention period.	Cellulose Derivatives (e.g., HPMC, Carboxymethylcellulose), Xanthan gum.
Stabilizers	By shielding the medication from oxidation and other types of chemical breakdown, stabilizers stop the substance from degrading.	Increase the formulation's stability	EDTA (Ethylenediaminetetraacetic Acid), Antioxidants (e.g., Ascorbic acid)
Antioxidants	Antioxidants preserve the stability and effectiveness of the medication by shielding it from oxidative deterioration.	Stop the oxidation of the drug's ingredients.	Ascorbic Acid, Sodium Metabisulfite, Tocopherols.
Humectants	Humectants prevent the nasal mucosa from drying out by keeping moisture in the formulation.	Maintain the formulation's moisture content.	Glycerine, Propylene Glycol, Sorbitol.
Surfactants	Surfactants improve drug dispersion and reduce surface tension, which increases absorption.	Improve the solubility and absorption of drugs.	Polysorbates (e.g., Tween 80), Lecithin, Sorbitan Monolaurate.
Preservatives	To prevent microbiological growth and guarantee the formulation's sterility, preservatives are added	Stop microbial development.	Benzalkonium Chloride, Phenyl Ethyl Alcohol, Parabens.
Buffering Agents	In order to improve medication	Keep the pH within the physiological range.	Sodium Phosphate, Citric Acid, Acetate Buffer.

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	stability and comfort, buffering agents aid in maintaining the formulation's pH.		
Chelating Agents	By binding metal ions that could catalyse oxidative processes, chelating agents stop deterioration.	Bind metal ions that aid in the breakdown of drugs.	EDTA, Citric acid.
Mucoadhesive Agents	Mucoadhesive agents extend the formulation residence time on the nasal mucosa, which enhances medication absorption.	Extend the duration of the drugs interaction with the nasal mucosa.	Chitosan, Hydroxypropyl Methylcellulose.
Solvents	The active pharmaceutical ingredient (API) is dissolved in solvents to produce a homogenous solution.	Disperse or dissolve the medication.	Water, Ethanol, Propylene glycol.
Co -solvents	Drugs that are not adequately soluble in the primary solvent are made more soluble by the addition of co-solvents.	Improve the solubility of medications that are poorly soluble.	Glycerine, Polyethylene glycol.
Osmotic Agents	By ensuring that the formulation is isotonic with nasal secretions, osmotic agents lessen irritation and enhance comfort.	Using nasal fluids adjust tonicity to be isotonic.	Sodium Chloride, Mannitol, Dextrose.

- *Different Types of Dosage Form:*

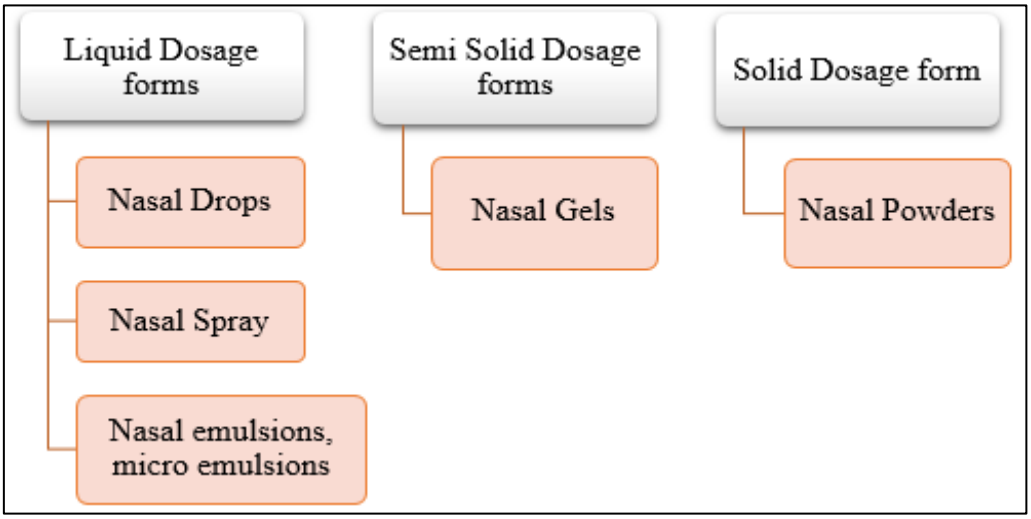

Fig 5 Different Types of Dosage Form

➢ *Liquid Dosage Forms:*

- *Nasal Drops:*

One of the easiest and most practical nasal administration modalities is the nasal drop. Nasal drops may not be appropriate for prescription medications due to the system's primary drawback, which is its lack of dosing precision. Human serum albumin has been found to be more effectively deposited in the nostrils by nasal drops than by nasal sprays. [40]

- *Nasal Sprays:*

Nasal sprays can be made using suspension or solution formulations. A nasal spray may provide a precise dose between 25 and 200 microlitres due to the availability of metered dose pumps and actuators. The choice of pump and actuator assembly depends on the viscosity of the formulation, the size and shape of the drug's particles, and the drug's suspension. [41]

➢ *Semi Solid Dosage form:*

Nasal medication delivery methods are typically designed using semi-solid systems, such as gels, ointments, and liquid systems using polymers that gel at specific pH changes.

- *Nasal Gels:*

Nasal gels are thickened liquids or suspensions with a high viscosity. There wasn't much interest in this technique until the precise dosage device was developed recently. A nasal gel's benefits include decreased post-nasal drip due to its high viscosity, decreased taste impact from less swallowing, decreased anterior formulation leakage, decreased irritation from the use of calming and emollient

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excipients, and improved absorption by targeting the mucosa. (42)

➢ *Solid Dosage form:*

Although these formulations are better suited for pulmonary drug administration and related applications because they may cover the vasculature within the nasal mucosa epithelium, solid dosage forms are also growing in popularity for intranasal medication delivery.

- *Nasal Powder:*

If solution and suspension dosage forms cannot be created, for instance because of poor drug stability, this dosage form may be created. The nasal powder dose form has the advantage of not having a better formulation preservative or stability. However, the solubility, particle size, aerodynamic characteristics, and nasal irritancy of the active medication and excipients determine whether the powder formulation is appropriate. Another benefit of this approach is the drug's local application. (43)

➢ *Marketed Nasal Drug Preparations*

Table 2 Marketed Nasal Drug Preparations

Drug Substance	Brand Name	Dosage form	Therapeutic use	Manufacturer	Reference
Oxymetazoline	Nasivion	Nasal spray/ Nasal gel	Relieves runny/stuffy nose, sinus pressure, reduces nasal swelling for better breathing.	Merck Ltd.	[44]
Fluticasone	Flonase	Nasal spray	Manages allergic rhinitis, hay fever, control sneezing, itchy/ runny nose, watery eyes, nasal blockage.	GlaxoSmithKline (GSK)	[45]
Ipratropium bromide	Atrovent	Nasal spray	Controls excessive runny nose(rhinorrhoea), no effect on congestion.	Boehringer Ingelheim	[46]
Cromolyn sodium	Nasalcrom	Nasal spray	Blocks histamine and leukotriene release, for allergic rhinitis, asthma, mastocytosis.	Sanofi	[47]
Xylometazoline	Otrivin	Nasal spray/ nasal gel	Provides short term relief from nasal congestion, due to cold, allergies, upper respiratory infections.	GSK Consumer Healthcare	[48]
Phenylephrine	Vicks Sinex	Nasal drops/ spray	Decreases nasal swelling, enhances airflow, eases congestion.	Procter & Gamble	[49]
Levocabastine	Livostin	Nasal spray	Nasal itch, mild congestion, runny nose.	Jansen-Cilag	[50]
Desmopressin	Minirin nasal powder	Nasal powder	Diabetes insipidus, bedwetting	Ferring Arzneimittel	[51]
Sumatriptan	Onzetra Xsail	Nasal powder	Migraine	Avanir Pharmaceuticals	[52]
Ayr Saline	Ayr Gel	Nasal gel	Moisturizing dry nasal passage	B.F. Ascher & Co.	[53]

- *Advanced Approaches in Nasal Delivery System*

Many factors have contributed to the creation of nasal formulations based on liposomes, microspheres, and nanoparticles for intranasal medication administration. These systems may additionally include enzyme inhibitors, nasal absorption boosters, or mucoadhesive polymers in addition to the drug to enhance stability, membrane penetration, and retention time in the nasal cavity.

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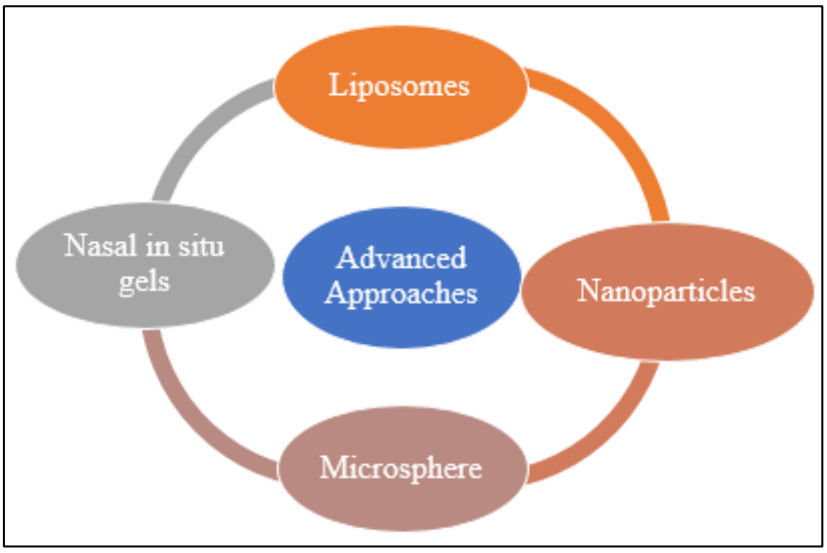

Fig 6 Advanced Approaches

✓ *Liposomes:*

Drugs and other chemicals can be integrated into liposomes, which are phospholipid vesicles made of lipid bilayers that enclose one or more aqueous compartments. The effective encapsulation of small and big molecules with a wide range of hydrophilicity and pKa values is one of the many benefits of liposomal drug delivery systems. In fact, by enhancing their membrane penetration, they have been shown to enhance the nasal absorption of peptides like calcitonin and insulin. [54]

✓ *Microsphere:*

Formulations for nasal medication administration have made extensive use of microsphere technology. Usually made of mucoadhesive polymers (chitosan, alginate), microspheres offer benefits for intranasal medication administration. Additionally, microspheres may prolong the medicine's action by sustaining drug release and shielding it from enzymatic metabolism. [55]

✓ *Nanoparticles:*

Solid colloidal particles with dimensions ranging from 1 to 1000 nm are called nanoparticles. They are made of macromolecular materials and can be employed therapeutically as drug carriers, where the active ingredient is dissolved, entrapped, encapsulated, adsorbed, or chemically bonded, or as an adjuvant in vaccines. Although nanoparticles' small size may provide a number of benefits, only the tiniest of them can enter the mucosal membrane through the paracellular pathway and in modest amounts because of the tight junctions, which are between 3.9 and 8.4.[56]

✓ *Nasal In-Situ Gels:*

Drug delivery systems that are in solution form before to being administered to the body but go through gelation to create gel after administration are known as in-situ gel formulations. Different polymers like chitosan, PVA, poloxamers, and Carbopol can be used to do this. [1]

- *Devices Used in Nasal Formulations:*

While some technologies can provide greater treatment benefits, nasal drug delivery solutions should be easy to use to prevent failures. To maximize pharmacokinetics, devices can be made to target a particular area of the nasal cavity. Effective nasal deposition, repeatability, robustness, tolerability, and a low respirable percentage are the desirable characteristics of nasal delivery system.

✓ *Drops Delivered with a Pipette:*

The pipette is one of the earliest nasal delivery tools. It works by sucking liquid into a glass dropper, putting the dropper into the nostril with the neck outstretched, and then applying pressure to the rubber to release the drips. It's fascinating to observe that metered-dose spray pumps are gradually replacing conventional drops. Nonetheless, low-cost single-dose pipettes made using the "blow-fill-seal" method are still often used for goods like saline and decongestants. [57] Despite their ease of use, pipette techniques have limitations since they require the patient to remain head-down and/or to extend their neck greatly in order to produce the requisite gravity-driven droplet deposition. [58]


Fig 7 Drop Delivered with a Pipette

➢ *Squeeze Bottles:*

The main purpose of squeeze bottles is to transport over-the-counter medications like topical decongestants. When the plastic bottle is pressed, the atomized medication is

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expelled from the jet exit, which is partially filled with air. The force used affects the dose and particle size, and when the pressure is released, bacteria and nasal secretions may be drawn into the vial. [59]

Fig 8 Squeeze Bottles

✓ *Metered Dose Spray Pumps:*

The majority of nasal products currently on the market employ metered-dose spray pumps. The pumps provide a good repeatability of emitted dose and plume geometry in in vitro experiments, and they usually release 100 µl every spray. These gadgets usually use an actuator, which is made up of a turbulence chamber and a nozzle orifice. By combining axial and rotational movements, the formulation spraying through the chamber produces a revolving cone that propels the formulation through the orifice quickly. Achieving an ideal deposition while limiting the percentage of tiny particles that can avoid the nasal channel and enter the lungs is the primary difficulty related to spray pump devices. [60]

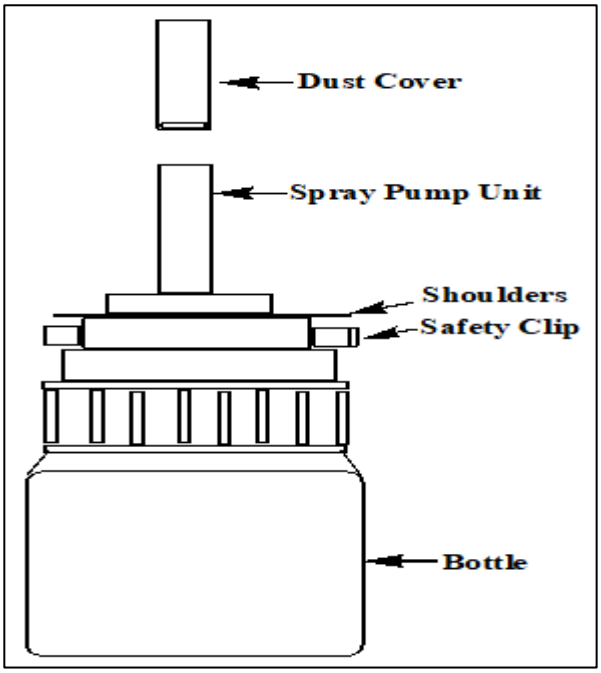

Fig 9 Metered Dose Spray Pump

✓ *Single and Double Dose Spray Devices:*

Because of their restricted dose control, metered-dose spray pumps are less appropriate for medications with a narrow therapeutic window, but they are suitable for the daily administration of pharmaceuticals over an extended length of time. For costly medications and vaccines meant for a single administration or for infrequent usage, when strict dosage control is necessary, single- or double-dose spray devices are preferred. The components of single- and double-dose spray devices include a swirl chamber, a piston, and a tiny vial. With the thumb on the actuator, these gadgets are grasped between the second and third fingers of 10 Cecilia de Barros et al. To ensure the repeatability of the actuation force and the properties of the released plume, certain devices employ a pressure point mechanism. [61] Examples of nasal pharmaceuticals that make use of this kind of technology include the commercially available flu vaccination Flu Mist and migraine drugs like Imitrex NS and Zomig. Due to sterile filling, these devices don't require preservatives; nonetheless, overfilling is required; in order to emit 100 µl, the device must fill with a volume of 125 µl. [62]

Fig 10 Single and Double Dose Spray Device

✓ *Pressurized Metered Dose Inhalers:*

The expansion of pressurized gas releases the pMDI particles at a high speed. pMDIs create nasal aerosols, which are used to deliver certain nasal medicines. After ozone-depleting chlorofluorocarbon (CFC) propellants were outlawed, there were fewer pMDI products available for nasal and pulmonary delivery. Hydrofluoroalkane (HFA)-based pMDIs have since taken the position of the former CFC pMDIs. The discomfort and dryness referred to as the "cold Freon" effect are caused by the rapid release of pMDI. It is said that HFA-based pMDIs are less uncomfortable than CFC-powered pMDIs because they generate particles at a slower rate. [63]

Fig 11 Pressurized Metered Dose Inhaler

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✓ *Insufflators:*

Insufflators are devices that deliver pharmacological substances for inhalation; they can be made with a tube or straw that carries the drug material, and occasionally they also include a syringe. Due to inadequate particle deaggregation, the realized particle size of these systems is frequently larger than the powder particle size, which leads to a significant coefficient of variation for initial deposition regions. Pre-dosed powder dosages in capsule form are used in several insufflator systems. (64)

Fig 12 Insufflators

✓ *Dry Powder Inhalers:*

Devices known as dry powder inhalers (DPIs) are used to provide an active medication in a dry powder formulation for either local or systemic effects through the pulmonary route. Often used to treat respiratory conditions like asthma, bronchitis, emphysema, and COPD, as well as diabetes mellitus, dry powder inhalers are bolus drug delivery devices that contain solid drug suspended or dissolved in a non-polar volatile propellant or in a dry powder inhaler that fluidizes when the patient inhales. (65) These have been used to treat diabetes mellitus as well as respiratory conditions such asthma, bronchitis, emphysema, and COPD. Typically, the drug is either stored in a patented form inside the inhaler or in a capsule for manual loading. When the inhaler is loaded or activated, the user inserts the mouthpiece into their mouth and inhales deeply while holding their breath for five to ten seconds. These devices come in a variety. Larger powder doses may cause coughing; therefore, the maximum amount that can be administered in a single breath is usually less than a few tens of milligram. (66)

Fig 13 Dry Powder Inhaler

V. DESIGN CHALLENGES IN NASAL DELIVERY SYSTEM

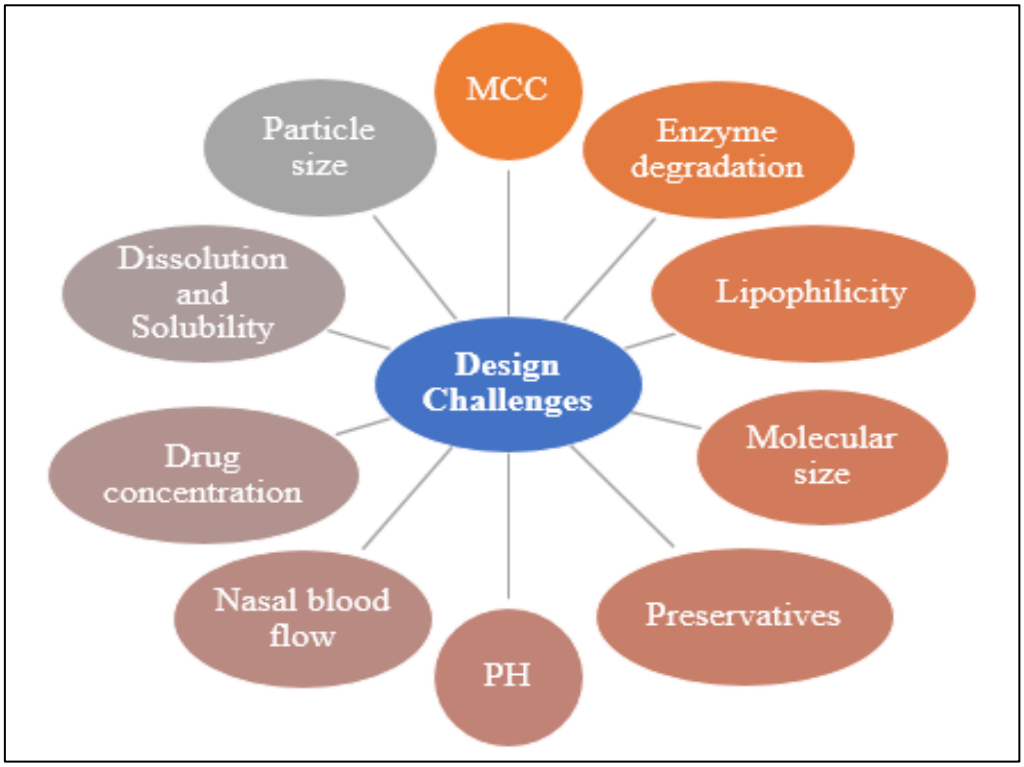

Fig 14 Design Challenges

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✓ *Mucociliary Clearance (MCC):*

One of the upper respiratory tract's duties is mucociliary clearance (MCC), which keeps allergies, bacteria, poisons, viruses, etc. from entering the lungs. The duration of medication interaction with epithelial tissue in the nasal mucosa affects drug absorption. When a chemical is given nasally, it is removed from the nasal cavity by MCC in about 21 minutes because mucociliary clearance, the nasal cavity's natural defense mechanism, removes compounds that stick to the nasal mucosa and leak into the nasopharynx. Drugs and additives used in nasal formulations have an impact on MCC; acetylcholine and methacholine agonists have been shown to increase ciliary activity, whereas salmeterol and isoprenaline receptor agonists have been shown to decrease it. MCC is reversibly inhibited by preservatives like chlorobutol. By decreasing MCC, drug permeation lengthens the duration that the drug and mucous membrane are in contact; an increase in MCC will result in a decrease in drug permeation. [67]

✓ *Enzyme Degradation:*

One of the main obstacles to the nasal absorption of medications is the nasal mucosal lining and the enzymes found in the nasal cavity. These enzymes have an impact on the trans nasal absorption of both hydrophilic and lipophilic drugs. The nasal cavity's proteins and peptides are poorly bioavailable. Drugs may be broken down by enzymes both in the nasal cavity's lumen and as they travel through the nasal epithelial barriers. The nasal mucosa contains a variety of enzymes, including aldehyde cytochrome P-450 dependent monooxygenase hormones. The metabolism of many xenobiotics is catalysed by cytochrome P-450 dependent monooxygenase. Numerous medications, including nicotine and phenacetin nasal decongestant, are metabolized by it in the nasal mucosa. Carboxylesterases are another type of enzymes that have been found to have the highest activity in nasal epithelia. [68]

✓ *Lipophilicity:*

As lipophilicity increases, the drug's penetration through the nasal mucosa typically increases as well. The nasal mucosa seems to be mostly lipophilic, albeit some of it is hydrophilic. Lipid molecules are crucial to the membrane's barrier function. Naloxone, buprenorphine, and testosterone are examples of lipophilic medications that are entirely absorbed by the intranasal route. When a drug's excessive hydrophilicity reduces its systemic bioavailability, the prodrug method can be helpful. [69]

✓ *Molecular Size:*

Drug absorption via the nasal route is influenced by molecular size. Nasal absorption of drug compounds with molecular weights larger than 1000 Dalton decreases dramatically. Because of the nasal epithelium's high permeability, relatively large absorption area, and porous and thin endothelial basement membrane, the rate of permeation is very sensitive to molecular size of substances with MW (≥300 Daltons). [69]

✓ *Preservatives:*

The majority of nasal formulations are aqueous, and some preservatives such parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA, and benzoyl alcohol are included to limit bacteria growth. Mercury-containing preservatives have an immediate and permanent impact on ciliary activity. [70]

✓ *Dissolution and Solubility:*

Drugs with low aqueous solubility require greater doses for intranasal administration because the permitted volume should be very low. This could make it difficult for a medicine to dissolve in the nasal cavity's fluid. The medication is eliminated and no absorption occurs if it is still in the form of particles. Medication should be sufficiently soluble in nasal secretions. [71]

✓ *pH:*

Drug penetration is influenced by the pH of the formulation and the nasal surface. The nasal formulation should be adjusted to the proper pH to minimize irritation, achieve effective absorption, and stop the growth of pathogenic bacteria. The formulation's pH should be adjusted between 4.5 and 6.5. The pH of nasal secretions is 5.5–6.5 in adults and 5.0–6.7 in newborns and children, while the pH of the nasal surface is 7.39. [72]

✓ *Nasal Blood Flow:*

Rich vasculature supplies the nasal mucosal membrane. Vasoconstriction and vasodilation of the blood arteries determine medication absorption and blood flow. Nasal blood flow is sensitive to both locally and systemically acting drugs and is influenced by a number of external and physiological factors, including ambient temperature, humidity, drug presence, trauma, inflammation, and psychological factors like emotion, fear, and anxiety. [73]

✓ *Drug Concentration, Dose and Volume of Administration:*

As nasal drug absorption increases at the delivery site, the drug concentration rises as well. This behaviour is more noticeable when medications are absorbed through passive diffusion, which is the main mode of drug absorption. Increased dosage and concentration have a detrimental effect on medication absorption and can occasionally cause nasal mucosal injury. Low dosages (25–200µl) are therefore recommended. [74]

✓ *Particle Size:*

Particles larger than 30 mm are eliminated because the nasal airway's cilia air turbulence causes a significant amount of air-mucosa contact time, which rises with a quicker respiratory rate. According to reports, particles less than 1 µm are inhaled and larger than 10 µm are deposited in the nasal cavity. [75]

VI. APPLICATIONS OF NASAL DELIVERY SYSTEM

➢ *Local Delivery:*

When compared to the oral route of administration, nasal distribution offers the least chance of systemic side effects, making it suitable for local (or topical) treatment. Consequently, nasal administration of relatively low dosages has fewer systemic adverse consequences. Well-known

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treatment medication classes include corticosteroids and antihistamines for allergic rhinitis, as well as decongestants for cold nose symptoms. (76)

➢ *Systemic Delivery:*

An efficient alternative to oral and intravascular routes for the systemic delivery of medications is intranasal administration. In fact, it appears to offer quick and prolonged drug absorption, and numerous research comparing intranasal drug delivery to oral and parenteral administration have been planned. As a result, the number of medications that are given as nasal formulations with the goal of achieving systemic effects has significantly increased. Analgesics like morphine, cardiovascular medications like propranolol and carvedilol, and hormones like levonorgestrel and progesterone are a few well-known examples. (77,78)

➢ *Central Nervous System Delivery Through Nasal Route:*

Drugs can be delivered to the brain through the intranasal route. (79) Drugs are delivered to the central nervous system (CNS) via the olfactory neuroepithelium. Alzheimer's disease, brain tumours, epilepsy, pain, and sleep difficulties have all been linked to nasal drug transport into the central nervous system (CNS). (80)

➢ *Delivery of Peptide- Based Pharmaceuticals:*

Due to their physical-chemical instability and vulnerability to hepato-gastrointestinal first-pass elimination, peptides and proteins often have a limited oral bioavailability. Pituitary hormones, insulin, and calcitonin are a few examples. When given as simple solutions, these peptides and proteins, which are hydrophilic polar molecules with a relatively high molecular weight, are poorly absorbed across biological membranes and have bioavailability in the range of 1-2% concentrations. We are mostly using absorption enhancers, such as surfactants, glycosides, cyclodextrin, and glycols, to raise the bioavailability in order to solve this issue. For these biotechnological compounds, the nasal route is turning out to be the most effective. (81)

➢ *Delivery of Non-Peptide Pharmaceuticals:*

Even in the absence of a permeation enhancer, tiny, nonpeptide lipophilic medications with a molecular weight of less than 1000 Daltons are efficiently absorbed via the nasal mucosa. Because nasal turbinates are present, the highly vascularized nasal membrane containing epithelium has a wide surface area and is easily accessible for medication absorption. (82) Progesterone, estradiol, propranolol, nitro-glycerine, sodium chromoglyate, and other medications with significant pre-systemic metabolism can be quickly absorbed through the nasal mucosa and have a systemic bioavailability. (83)

VII. CONCLUSION

Nasal drug delivery systems represent a groundbreaking non-invasive method that boosts treatment efficacy, especially for CNS conditions, by capitalizing on the nose's structural benefits and sophisticated formulations to tackle absorption hurdles. Even with obstacles such as mucociliary clearance and constrained volume capacity, the smart application of absorption promoters, mucoadhesive polymers, and nano-based carriers—like liposomes, microspheres, and nanoparticles—in forms such as sprays, gels, and powders guarantees prolonged drug release, swift BBB traversal, and better patient adherence compared to conventional delivery methods. Looking ahead, breakthroughs in delivery devices and compatible excipients will broaden uses for peptides, proteins, and brain-related treatments, establishing intranasal routes as a vital pillar in contemporary pharmaceutical practice.

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