

A Review on Recent Trends in Nasal Drug Delivery System

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ABSTRACT

Intranasal administration of antihistamines, antibiotics, vasoconstrictors, and decongestants has been used for many years to induce a local effect on the mucosa. These medications have the advantage of systemic bioavailability when self-medicated. When compared to oral delivery, nasal administration is more effective. Traditional nasal drug delivery systems, being superior to oral or injection administration, challenge limitations that maximize their efficacy and applicability. The intranasal route has gained popularity as a method for systemic administration of vaccines, hormones, peptides, and other medicines. Intranasal medication delivery, once limited to the treatment of rhinitis and nasal congestion, is increasingly obtaining popularity for the administration of a vast range of medications. Nasal drug delivery alternatives are being considered as feasible alternatives to established systemic drug administration routes. This is due to the nasal epithelium's high permeability, which allows for a greater molecular mass around 1000 Da, as well as the quick rate of drug absorption is often like that of intravenous injections, alongwith plasma drug profiles that are almost identical.

Keywords:-Vasoconstriction; Nasal drug delivery; Bioavailability; Congestion; Absorption rate.

Introduction

The nasal route was introduced as a viable systemic drug distribution substitute to other conventional drug distribution routes in the early '1980s. This Nasal delivery route has been given a new lease, on life after being used for thousands of years¹. It's a good way to

administer drugs like proteins and peptides, which are active at low dosages and have little oral bioavailability².The nasal mucosa is permeable to more chemicals than the intestinal tract due to lack of pancreas, stomach enzymatic activity, less degradation by gastric contents, and neutral pH of the nasal mucus. It has been proposed as a possible approach for achieving higher and faster levels of medication absorption³.Nasal therapy is also known as "NASAYA KARMA" in Ayurvedic schools of Indian medicine is an approved kind of treatment⁴.The nasal delivery can be useful, for systemic pharmaceutical administration as well as for local effects. Researchers are still working on developing an appropriate nasal drug delivery method⁵.Many steps have been taken in the past years to increase the retention time of medication formulation in the olfactory region in enhancing nasal drug absorption. The nasal mucosa's high vascularization and permeability stimulated researchers' interest in employing it as a method for systemic medication delivery⁶.To ensure a local or systemic action, the drug to be administered must be adjusted to particle size, concentration, and chemical form depending on the desired site of drug action. Bypassing the first-pass metabolism, this pathway provides a porous endothelium membrane, broad surface area, high blood flow, and easy accessibility⁷.Nasal preparations include nasal sprays, nasal drops, nasal ointments, nasal creams, and nasal aerosols according to the marketed formulations of nasal products. Due to their extended retention duration, nasal ointments and creams are primarily used in the treatment of nasal bacterial infections and the cure of nasal blockage or congestion⁸.

The benefits and constraints of nasal therapies, as well as the physiology of the nasal passage, are briefly discussed in this systematic review. Advantages, nasal absorption mechanism, nasal absorption obstacles Nasal drug absorption factors and techniques, nasal drug administration applications.

Morphology and Physiology of Nose

The nose channel travels from the nasal vestibule to the nasopharynx which is 12-14 cm long. It is divided into three sections: respiratory, olfactory, and vestibular (Figure 1). The nasal area is 16-19 cm³ in volume and 180 cm² in surface area, having two chambers (nostrils) divided by the septum of the nose⁹.The vestibular area, which filters particles from breathed air, is positioned at the front aperture of the nasal passages. In this region, however, drug administration and absorption are of the utmost importance. Hairs cover this area, filtering the air and preventing airborne pollutants from entering the respiratory system¹⁰.The respiratory region has a surface area of around 130 cm² which is big and vascularized. Most medication

absorption takes place in this area. it is covered with pseudostratified epithelium and coated with sticky mucus that flows towards the posterior passages of the nasal cavity due to cilia rhythmic motions¹¹. The olfactory pathway covers a total surface area of around 15 cm², which is vital for delivering drugs to the cerebral-spinal fluid and brain. It's made up of lamina propria and thick connective tissue¹². Nasal mucosa thickness varies between 2-4 mm. The sticky mucus layer 5 m protects the epithelial cells that line the nose canal, trapping foreign particles. Water accounts for 95% of mucous secretion, mucin for 2%, salts for 1%, proteins such as immunoglobulin, albumin, lactoferrin, lysozyme for 1%, and lipids for 1%. Mucus secretion also contains IgA, IgE, and IgG antibodies¹³. The nasal secretion's pH ranges from 5 to 6.5. Ciliary stimulation clears the mucous membrane in the nose canal, and mucus is produced 4 to 6 times every hour. Mucus passes through the nose at a rate of 5-6 mm/min¹⁴.

Nasal Mucosa

The nasal lining is made up of the same pseudostratified ciliated epithelium as most of the respiratory system. Each cell has up to 200 cilia, the tips of which are found in the superficial gel layer¹⁵. In the anterior portion of the superior and middle eustachian tubes, where there is the most contact with the inspired air, tumor growth with cuboidal cells without cilia can occur¹⁶.

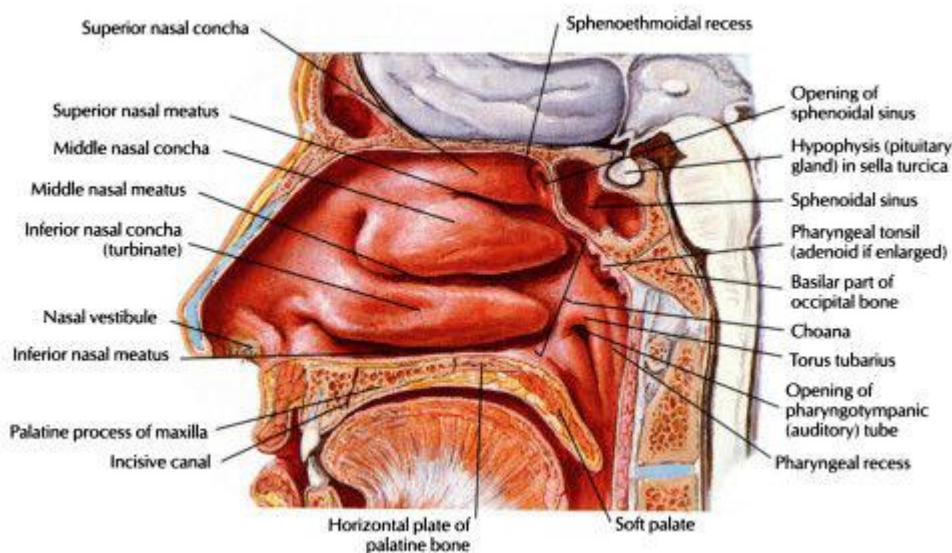


Figure 1: Structure of nasal mucosa

Table 1: Characteristics of the Nasal Mucosa

Parameters	Nasal Mucosa
Surface area	150-180 cm ²
Thickness	1-2 mm

Endothelial basement membrane	The porous and thin structure of the endothelial basement membrane possesses no restriction to the entry of the drug molecule into the systemic circulation
Permeability Epithelium	The nasal mucosa possesses porous epithelium
Vascularity	Arterial supply: External and internal carotid artery, maxillary artery via a sphenopalatine artery

Advantages

1. Self-medication is easier with easy access and needle-free drug delivery without any requirement for skilled people, which promotes patient compliance as compared with parenteral approaches¹⁷.
2. Drugs having low molecular weight, especially lipophilic drugs, penetrate the nasal mucosa¹⁸.
3. Because of the relatively high vascularization and wide absorption surface, the drug absorbs quickly and has a quick onset of effect. The T_{max} of fentanyl following nasal delivery was less than or comparable to 7 minutes as compared to intravenous [i.v] administration. As an alternative to parenteral administration, intranasal delivery of a relevant medicine would be beneficial in emergency therapy³.
4. Avoid the gastrointestinal tract's harsh environmental conditions (drug chemical and enzymatic degradation)²⁰.
5. Nasal medication delivery avoids hepatic first-pass degradation, allowing for a dose reduction when compared to oral drug delivery²¹.
6. Opportunity for drug delivery to the nervous system directly through the olfactory epithelium, bypassing the blood-brain barrier²².
7. Nasal administration is an alternative to parenteral administration, particularly for proteins and peptides²³.
8. The vaccine is delivered directly to lymphatic vessels, and secretion immune reaction is induced at a proximal mucosal site²⁴.
9. Case convenience and compliance is bettered
10. The mucous membrane allows for good penetration of low molecular weight medications, especially lipophilic ones.

Mechanism of Drug Absorption

The mucus is the principal mechanism in the transport and permeation of a drug via the nasal passage. Mucin which is a protein derived from mucus, can adhere to solutes and so influence the rate of diffusion. The mucus layer must pass through the absorbed medications from the nasal cavity²⁵.

There are two mechanisms:

Paracellular- It contains the paracellular route, which is an aqueous transport mechanism, but which is inactive and slow. Molecular weight for water-soluble compounds and intranasal absorption has an inverse log association. Bioavailability is low for drugs having a molecular weight greater than 1000 Daltons²⁶.

Transcellular- It involves lipoidal transport, also termed as the transcellular process, and is responsible for the distribution of lipophilic drugs with the rate depending on their lipophilicity, Drugs can also be delivered through the cellular membrane via a carrier-mediated route or by causing tight junctions to open²⁷.

Barriers to nasal absorption

The nasal medication delivery system is thought to be a cost-effective and option for formulations experts as it provides easy and simple formulation procedures. The therapeutic effectiveness, safety and toxicities of intra-nasally delivered medicinal products are affected by a variety of circumstances²⁸.

Factors related to barriers for drug absorption

Bioavailability: The bioavailability of polarized Drugs is often low, ranging from roughly 10% of low molecular weight pharmaceuticals to less than 1% with peptides like insulin and calcitonin²⁹. The low permeability of cell membrane has been the most important factor restricting the nasal intake of polar medications, specifically big molecular mass polar pharmaceuticals like peptides and proteins. Drugs can penetrate through the epithelial cellular membrane in one of three ways: receptor-mediated or vesicular via receptors, transcellular by simple gradient of concentration, and paracellularly via tight connections between cells. Polar medicines with molecular weights less than 1000 Da are more likely to get through the membrane via the latter pathway³⁰.

Despite tight junctions that constitute a dynamic system that expands and also close to a degree as required, the average size of these pathways is on the order, of tens of nanometers, preventing the transport of bigger molecules. Endocytosis transport allows proteins and larger peptides to pass through the nasal cell wall, but only in small numbers. Co-administration of

absorption-enhancing medications with such polar medicines can considerably improve nasal absorption³¹. Agents mainly used for trans nasal involvement are bile salts and bile salt derivatives (sodium deoxycholate, sodium taurodihydrofusidate, sodium glycocholate), Surfactants (laureth 9, sodium lauryl sulfate), phospholipids (DDPC, lysophosphatidylcholine), fatty acids and fatty acid derivatives (linoleic acid) and various cyclodextrins (dimethyl-cyclodextrin), chitosan and derivatives like poly-L-arginine, poly-L-lysine. These enhancers work in a number of ways but most of them work by changing the permeability of the epithelial cell layer by modifying phospholipid bilayers, leaching proteins from the membrane, or even removing the mucosa's outer layer. Some of these enhancers also have an effect on tight junctions and/or act as an inhibitor of enzymatic degradation³².

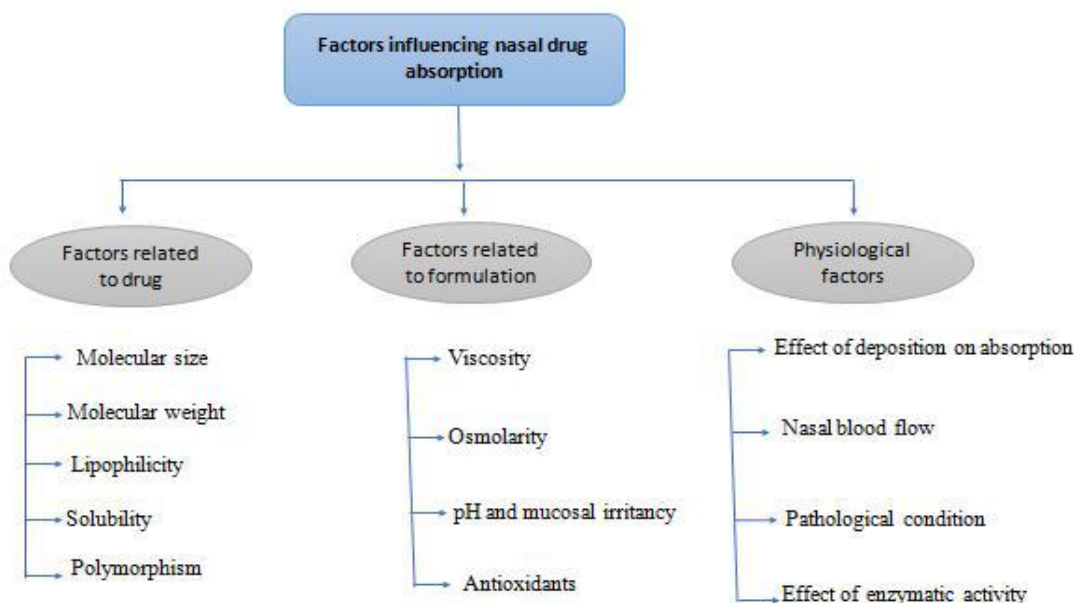
Low transfer through the membrane: The important feature is poor cellular membrane transport which refers to the mucociliary clearance mechanism's general quick removal of supplied formulation, from nasal passage. This is especially true for medications that are difficult to absorb via the nasal membrane³³. Non-mucoadhesive solution and powder formulations have been proven to have a clearance half-life of 15–20 minutes. Deposition of the formulation in the anterior section of the nasal pathway, as opposed to depositing further posterior in the nasal passage, has been suggested to reduce clarity and improve absorption. In comparison to nasal drops, which are administered to a broader region further behind in the nasal route, most of the nasal sprays of different brands have been proven to transport the formulations to a restricted area in the anterior section of the nasal pathway³⁴. To combat the fast mucociliary clearance, bioadhesive substances are used for the formulations. By depositing the formulation in the forward, less ciliated portion of the nasal pathway, the clarity can be minimized, resulting in good absorption³⁵.

Enzymatic Degradation:

Another component that contributes to peptide and protein bioavailability over the mucosa of the nose, but is typically overlooked, is the likelihood of enzymatic breakdown of the molecule, in the nasal cavity lumen or during transit through the epithelial layer³⁶. Exopeptidases like mono and diaminopeptidases could cleave peptides at their C and N terminal and endopeptidases like cysteine and serine can attack inner peptide bonds at both sites. Enzyme inhibitors and enzyme overload could be used to break through this barrier. In conclusion, the nose has distinct advantages as a medication administration site. Low permeability for high molecular weight and polar medications, quick clearance of the delivery system from the nasal cavity, and probable biological drug breakdown in the nostrils may all

be issues. Various techniques, like as the use of absorption enhancers and bioadhesive systems, can be used for addressing these issues³⁷.

Factors influencing drug absorption through nasal cavity



Factors related to drug

Molecular Size:

The drug's molecular size seems to have had an impact on its absorption through to the nose. The molecular weight and the drug penetration are directly related in lipophilic medicines, but to the contrary is true for water-soluble substances. For molecules with MW 300 Daltons, the rate of permeation is dependent upon the size of the molecules³⁸.

Molecular weight:

A linear inverse relationship between medication distribution and molecular weight has been documented up to 300 Da. Unless distribution enhancers are used, absorption reduces dramatically when the molecular weight exceeds 1000 Da. The shape is also important, Linear particles absorb less energy than cyclic-shaped particles³⁹.

Lipophilicity:

The penetration of the chemical via the mucosa of the nose increases as the lipophilicity of the particles increases. Despite, the fact that the mucosa of the nose has some hydrophilic properties it appears that these mucosa are largely lipophilic in nature with the lipid domain playing an essential part in the barriers function is based on these membranes. In one study, lipophilic compounds alprenolol and propranolol were found to be well absorbed from the mucosal surface, in contrast to the hydrophilic drug metoprolol, because lipophilic substances

can divide into the lipid layer of the endothelium membrane and permeate into and pass the cells in the cytoplasm, they can easily cross biological membranes through the transcellular route⁴⁰.

Solubility:

The molecularly dispersed form of medication at the absorption site may cross the biomembranes, drug dissolution is a prerequisite for any drug absorption. As a result, before nasal absorption, the medicine must be dissolved in the nasal cavity's watery fluids. As a result, the optimum aqueous drug solubility is critical for adequate contact with the nasal mucosa and posterior absorption. Drug solubility, on the other hand, has an impact on the absorption profile. As a result, medications that are poorly soluble in water and/or require high doses may be a concern. This can be overcome by increasing the water solubility of the medication⁴¹.

Polymorphism:

In nasal drug release and product design, determining the polymer form of medication is a crucial part to consider. Different polymorphs have an impact on medication breakdown and absorption through the nasal pathway. Various polymorphic versions of medication have various levels of nasal mucus membrane penetration. The stability and purity of polymorphic forms must be considered in the nasal compositions. The drug's delivery to the brain is regulated by the nasal mucosa's pH and the drug itself. For the avoidance of nose irritation, bacterial growth, and mucosal damage, the formulation's optimal pH should be between 4.60 and 6.50. Only a portion of the medicine that is not ionized can pass through the nasal mucosa⁴².

Factors Related to formulations

Viscosity:

The viscosity of the nasal spray affects spray characteristics such as spray geometry and droplet size as well as nasal deposition. When compared to viscous formulations, nasal formulation along with reduced viscosity tends to settle posterior to the nose. Furthermore, increased viscosity was linked to narrower plume angle and larger droplet size, resulting in a small spray region. The permeability of medications is altered when more viscous preparations involve typical activities such as mucociliary clearance or ciliary beating⁴³.

Osmolarity:

The isotonic solution of formulations can affect drug administration. In presence of hypertonic solutions, epithelial cell shrinkage has been reported⁴⁴. Hypertonic saline solutions

decrease or cease ciliary function as well. A hypotonic solution has the same effect as low pH solutions⁴⁴.

pH and mucosal irritancy:

The penetration of medicine is influenced by the pH of the formulation as well as the pH of the nasal surface. The pH of the nasal formulation should be adjusted to 4.5–6.5 to avoid nasal discomfort. It results in effective drug permeation and prevents the formation of microorganisms, in addition to minimizing discomfort⁴⁵.

Antioxidants:

Antioxidants rarely cause nose irritation or interfere with medicine absorption. Antioxidants include sodium bisulfite, sodium metabisulfite, butylated hydroxyl toluene, and tocopherol⁴⁶.

Physiological Factors

Effect of Deposition on Absorption:

The formulations are deposited in the front section of the nostril, which allows for a longer length of nasal resident duration. The front region of the nostril has low permeability, but the posterior area of the nose has a shorter resident time and higher permeability⁴⁷.

Nasal Blood flow:

The flow of blood to the mucous layer of the nose is abundant. Nasal drug administration is affected by blood flow since, nasal relaxation and congestion regulate the fall and rise in drug penetrated amount, respectively. As a result, it's possible to deduce that parasympathetic activation causes greater permeability⁴⁸.

Pathological conditions:

The condition which influences the efficacy and speed of mucociliary clearance, nasal secretions, and irritation in the nasal mucosa such as the common rhinitis, cold, nasal polyposis, and atrophic rhinitis can alter the Drug absorption profile⁴⁹.

Effect on Enzymatic activity:

Nasal absorption of drugs avoids the hepatic first-pass metabolism and gastrointestinal impact. Due to the availability of a wide spectrum of biochemical enzymes in nasal cells, they may be considerably digested in the nasal passage lumens or during passing over the nasal epithelial barrier. Pharmaceuticals such as nicotine, cocaine, alcohols, progesterone, and decongestants are metabolized by oxidative phase I enzymes (e.g., Cytochrome P450 isoenzymes⁵⁰). Distinct species have different populations and/or activity of nasal enzymes. However, based on the quantity of tissue involved, the degree of activity for nasal enzymes appears to be lower than for those in the gastrointestinal tract or liver⁵¹.

Effect of pathological condition:

Nasal pathological diseases include rhinitis (allergic and non-allergic), nasal polyps and cancer, and ordinary colds can all affect permeation from the nasal passage in various ways. Bleeding, increased mucus flow, nasal blockage, and crusting are all symptoms of nasal conditions. A rhinovirus infection has been shown to cause epithelial cell sloughing and epithelial layer damage in vitro. A nasally delivered medicine may be washed away by excessive nasal discharge before it can be absorbed⁵².

Strategies To Improve Nasal Absorption

Various measures have been used to increase the drug's bioavailability in the nasal mucosa, including

1. To increase the resident time in the nasal cavity
2. To improve absorption by the nose
3. To change the physicochemical qualities of medication by changing its structure.
4. To enhance the absorption and bioavailability of the formulation any one or a combination of the above procedures can be applied. Several ways have been used to enhance drug administration through the nose, including:

Mucociliary clearance:

Mucociliary clearance is the process of removing foreign materials and substances as rapidly as possible from the nasal mucosa. One method for delaying clearance is to apply the medicine to the anterior region of the nasal cavity, which is largely controlled by the sort of dosage form used¹⁵. The preparation could alternatively be made with polymers like methylcellulose, hydroxypropyl methylcellulose, or polyacrylic acid, which enhances viscosity and functions as a bioadhesive with mucus. Increased residence time does not always imply increased absorption; this principle can be shown using an insulin solution containing carbopol and carboxymethyl cellulose of similar viscosity (CMC). Carbopol improves insulin absorption, whereas CMC solution does not enhance the administration of insulin. In the case of Carbopol, it increases distribution via opening intracellular connections. Using biodegradable microspheres as a drug delivery carrier is another potential option to extend nasal residence duration. In the presence of water, biodegradable microspheres swell, increasing the viscosity. As a result of this event, the nasal residence time increases⁵³.

Permeation enhancers:

Permeation enhancers are mainly used to increase the active ingredient's absorption...

Penetration enhancers work by the following mechanisms: Reduce mucociliary clearance; Open tight junctions; Reduce mucus elasticity or viscosity and Solubilize or stabilise the medication. Absorption enhancers work by enhancing the rate at which the medicine passes via the nasal mucosa. Different enhancers work by, changing the composition of epithelial cells, they must do so without harming or permanently modifying the nasal mucosa⁵⁴.

The following are the general requirements for an ideal penetration enhancer:⁵⁵

- 1 It should result in a significant increase in drug permeation.
2. There should be no permanent injury or alteration to the tissues.
3. It should not be harmful and irritate the skin.
4. It should be helpful even when taken in little quantities.
5. When absorbing is required, the impact should occur
6. The effect should be transient and reversible.

Prodrugs:

The bulk of intranasal medications is given as solutions or powders that must be digested before they may be absorbed. Although lipophilic drugs are not water-soluble, they are easily transported across biomembranes. In order to make an aqueous nasal formulation with a sufficient concentration, they need to be supplied as a prodrug with a more hydrophilic character. As soon as prodrug enters the bloodstream. It must be transformed back to the original medication. Synthesized several L-dopa drug candidates and observed that their solubility was much increased over the parent drug, permitting the production of effective nasal formulations⁵⁶. Testosterone which is also a water-soluble produced a similar result. Polar medicines that are extremely hydrophilic, on the other hand, may not be able to cross the blood-brain barrier. As a result, membrane penetration may be boosted if they are supplied as a prodrug with a better lipophilic character⁵⁷.

Co-Solvents:

Cosolvents can be used as an alternative to prodrugs to increase medication solubility. The most widely used co-solvents in the intranasal formulation are ethanol, glycerol, polyethyleneglycol, and propylene glycol and they may be very essential since they are pharmaceutically acceptable, non-toxic and non-irritant to the nasal pathway⁵⁸.

Nasal enzyme inhibitors: Drug metabolism in the nose can be slowed along with the use of enzyme inhibitors. In the production of peptide and proteins compounds, enzyme inhibitors such as proteases and peptidases are routinely used. Fusidic acid and Salts derivatives, for example, block enzymes as a result increased bioavailability and medication absorption.

Additional enzyme inhibitors such as aprotinin, trypsin, amastatin, bestatin, borovaline and boroleucin are commonly used for enzymatic activity⁵⁹.

Structural modification:

The most profitable method to promote nasal permeation is to improve the structure of a drug without changing pharmacological effectiveness. By modifying the physicochemical qualities of treatment, such as molecular weight, molecular size and solubility, chemical modification of drug molecules and P_{ka} has been widely employed to increase medication absorption by the nose. When salmon calcitonin was chemically changed to ecatonin (where the C-N link replaced the S-S bond), ecatonin had a good bioavailability other than salmon calcitonin⁶⁰.

Applications of Nasal Delivery

Nasal decongestant:

The nose is used to treat localised problems with low therapeutic doses and minimal systemic side effects. Local pathological problems in the nose are treated with low molecular weight water-soluble or hydrophobic medicines. Nasal decongestants, such as xylometazoline, are also used to treat colds through the nose⁶¹.

Systemic Effects:

When a quick response is required, like in the treatment of migraine, nostril administration is suitable for acids labile medicines, peptides, and proteins⁶². Because of their higher molecular weight and polarity, peptide and protein medicines have less bioavailability (1–2%), resulting in poor permeation via the nasal mucosal membrane. Progesterone and propranolol bioavailability via nasal epithelium, on the other hand, is comparable to parenteral delivery⁶³. Less bioavailability can be increased by including permeation enhancers in the formulation and utilising bioadhesive agents to extend the drug's contact time with the mucosal membranes. In rats, utilising 0.1 percent N-succinyl chitosan as a permeation enhancer resulted in a considerable increase in the higher relative bioavailability of isosorbide dinitrate (69.85 percent) then the control groups (43.32 percent) and the 0.5 percent chitosan (55.36 %) ⁶⁴.

Vaccine Delivery:

Vaccines and their use in the treatment of respiratory illnesses via the nose have been studied. Because immune system molecules are located in the mucosal surface, the respiratory system is the body's initial line of defence against infections. Lymphocytic tissue enriches the nasal mucosa. It boosts system levels of particular nasal secretory immunoglobulin A

and immunoglobulin G as well as local immune cells, giving you more resistant to microbial invasion⁶⁵.

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