From Lab to Lungs: Nasal Drug Delivery in Modern Medicine

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Abstract: Nasal delivery has the most appropriate option for topical treatment of local conditions affected the nose and paranasal sinuses, like rhinosinusitis and allergic and non-allergic coryza. Additionally, the nose has considered to be a desirable way of administration for systemic drugs and needle-free vaccinations, specifically when quick absorption and effectiveness have required. Also, the nasal administration may help to address problems including poor bioavailability, slower absorption, drug degradation, and adverse effects in the GI (gastrointestinal) tract by avoiding the liver's first-pass metabolism. intranasal administration has the preferred method of administration for drug delivery to the central nervous system, systemic as well as locally. This article describes the important characteristics of nasal physiology, anatomy, and histology as well as the pharmacological, physicochemical, and biological considerations that need to think carefully while developing a nasal spray formulation. Formulation design and development, characterisation are also discussed in brief. The review also examines the benefits and challenges associated with nasal drug delivery.

Keywords: Nasal spray, Device for drug delivery, Formulation of nasal spray, Nasal anatomy.

INTRODUCTION

In the recent decades, nasal distribution of medications has been seen as a potential way of administration to attain higher levels of drug absorption and bioavailability. The nose provides simple access to a wide mucosal surface that is ideal for the administration of medications and vaccines. The systemic effects of the medications delivered through this method provide an alternative to the parenteral distribution of the medications, which is sometimes inconvenient, as well as oral delivery of the medications, which may reduce bioavailability. The nasal route has proven to be beneficial for drug administration due to the nasal epithelium's highly permeable monolayer, the submucosa abundant vascularization, and the avoidance of hepatic presystemic metabolism. Nasal spray along with aerosol products have designed to deliver a spray containing a metered dose of the active ingredient that has dissolved or suspended in solutions or mixtures of excipients. They are packaged within non-pressurized/pressurized dispensers intended to deliver medication to the nasal cavity. Tyzine (tetrahydrozoline hydrochloride) nasal solution which has the first nasal spray medicine approved by The Food and Drug Administration (FDA) in 1954 to treat nasal congestion caused due to sinusitis, hay fever, cold. Since then, allergic conditions affecting the nasal cavity, such as stuffy nose, coryza, rhinosinusitis, and associated allergic reaction, are typically treated with localized nasal drug delivery. Nowadays a range of formulations like nasal drop, nasal spray, nasal powders, nasal gels, nasal inserts and others which have been used for administration of drug by nasal route. Now drugs can be delivered directly to the central nervous system by using specially-designed devices that can target the olfactory region of the nose when applying sprays or powders [1,2,3,4,11].

1. Nasal anatomy and physiology: [1,5,11]

The mucous layer and hairs that line the nasal cavity are important for trapping infections and inhaled particles. The nasal cavity of humans has a total capacity of 15-20 mL and a surface area of around 150 cm2. The nasal halves are divided into four areas: the respiratory region, the olfactory region, the nasal vestibule, and the atrium.

a) Nasal vestibule: The vibrissae, or nasal hairs, line the nasal vestibule and filter inhaled particles. High resistance against harmful environmental compounds can be achieved by having nasal vestibular characteristics, however this also makes it extremely difficult to absorb substances, including drugs.
b) Atrium: The space in between the respiratory region and the nasal vestibule is called the atrium. Its posterior region is made up of pseudostratified columnar cells showing microvilli, whereas its anterior half is composed of a stratified squamous epithelium.
c) Respiratory Region: It is divided between three projections from the lateral wall: the superior, middle, and inferior turbinates. The basement membrane, lamina propria, and epithelium

made up the nasal respiratory mucosa, which is considered to be the most important region for systemic drug delivery. The respiratory area serves to warm, humidify, filter, and remove debris from the air that is inhaled. It also provides the nasal epithelium with enzymatic and physical defence against many external substances, including medications.

d) Olfactory region: The olfactory region is situated in the roof of the nasal cavity and stretches a short way down the Septum and lateral wall. It is pseudostratified and has specific olfactory receptor cells that are important for the sense of smells.

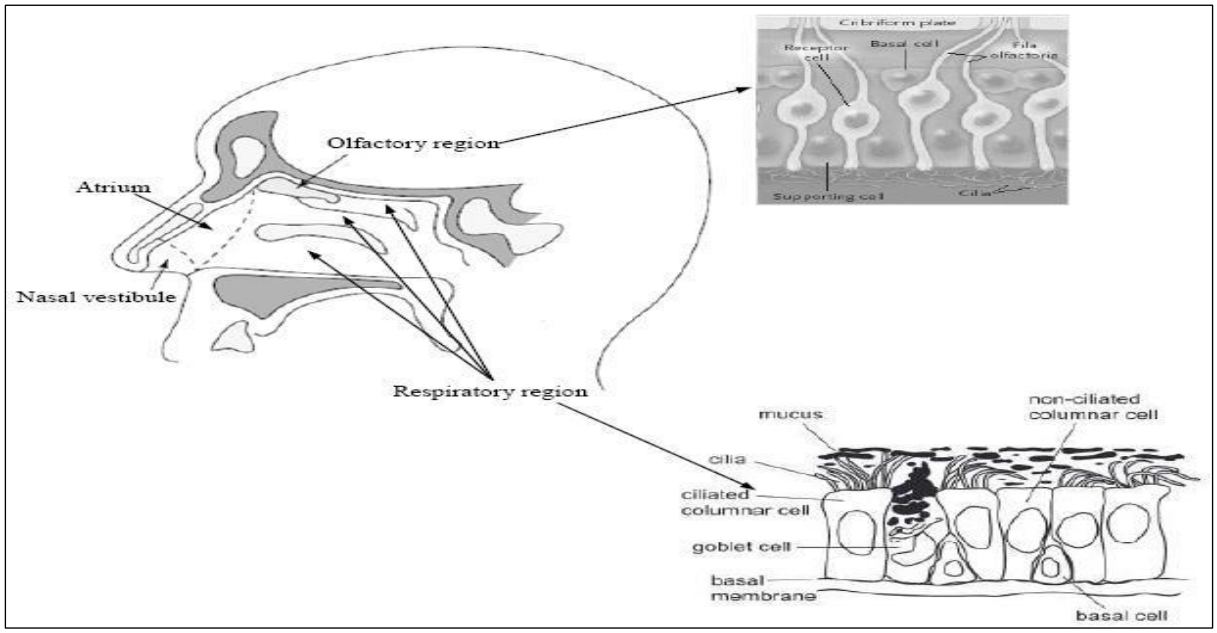

Fig-1: Anatomy and histology of human nasal cavity

2. Device for drug delivery:

A number of different devices are available for nasal drug delivery. Since the formulation to be administered in the form of a powder, liquid, or aerosol, the device should be able to provide several dosage forms. The optimum performance is achieved by nasal drug delivery systems when consideration is given to spray characteristics, mucociliary clearance, deposition, dissolution, and absorption. The design of nasal delivery devices and their functions should protect the nasal passageway and lungs from a variety of harmful exposures [5,6,7,19].

Drug product delivery and device development:

The nasal cavity has limitations, such as low permeability for specific drugs, such as proteins, peptides, hydrophiles, and nucleotides, rapid mucociliary clearance, and biodegradation, even with the apparent advantages of intranasal drug administration. For the production of safe and effective intranasal drugs, drug delivery and device development are essential. The medicine, the delivery vehicle, and the administration devices work together to control drug delivery through the nasal route. Drugs with a low molecular weight (less than 300 Da) can easily flow through the nasal membrane's aqueous channels, whereas drug with a high molecular weight cannot. Since the nasal mucosa is lipophilic, lipophilic drugs can penetrate it more easily. Hydrophilic drugs may be administered in the form of a prodrug. Low bioavailability of peptides and proteins is due to their enzymatic degradation during epithelial layer crossing. Enzyme inhibitors or protective shells such as liposomes and micelles can be used to prevent such enzymatic breakdowns. The drug's contact time with the nasal mucosa can be extended by incorporating a viscous delivery vehicle, increasing the drug's penetration time. In order to avoid nasal irritation the formulation's pH should be adjusted to a value between 4.5 and 6.5. For hydrophilic or high molecular-weight drugs to pass across the nasal membrane in sufficient amounts for therapeutic usage, a nasal absorption enhancer would be required. CPE-215®, Intravail®, ChiSysTM, PecSys™, and CriticalSorb™ are examples of the absorption enhancers that are currently in the development stage for a variety of drugs by CPEX Pharma, Aegis Therapeutics Archimedes Pharma Ltd., and Critical Pharmaceuticals Ltd, respectively [5,8,9,20].

3. Factors Influencing Nasal Drug Absorption: [1,11,12,13,18]

➢ Biological Factors:

a) Structural features: the nasal physiology consists of nasal vestibule, atrium, respiratory area, olfactory region and the nasopharynx. These organelles as well as the type and number of cells as well as cell density present in that region influence the permeability. Formulations of drugs with absorption enhancers increase the permeation of compounds.

b) Biochemical changes: The nasal mucosa acts as an enzymatic barrier to the transport of drugs due to its abundance of oxidative and conjugative enzymes, as well as peptidases and proteases. Different peptide drugs are presystemically degraded by protease and peptidase, which results in a decrease in their penetration.

➢ Physiological factors:

a) Blood supply and neuronal regulation: The nasal mucosa is greatly permeable and its blood supply is under the influence of the autonomous nervous system. This leads to variations in the amount of drug absorbed.

b) Nasal secretions: Nasal secretions are secreted by the anterior serous and seromucous glands. The permeability of drugs through the nasal mucosa is affected by the viscosity of nasal secretions, the solubility of drugs in nasal secretions and the pH of the nasal mucosal surface.

c) Mucociliary clearance and ciliary beat frequency: Mucociliary clearance, the nasal cavity's natural defense mechanism, removes substances that stick to the nasal mucosa and drains into the nasopharynx in the GIT. Any substance supplied by the nose is cleared from the nasal cavity by mucociliary clearance in about 21 minutes.

d) Pathological conditions: Mucociliary dysfunction, hypo- or hypersecretions and prickliness of the nasal mucosa occur due to pathological conditions and can affect drug absorption.

e) Environmental conditions: It has been reported that a linear increase in ciliary beat frequency occurs with temperature rise, with a moderate drop in the rate of MCC occurring at 24°C.

f) Membrane permeability: Membrane permeability affects drug absorption when administered via the nasal route.

➢ Physicochemical Properties of Drugs:

a) Molecular weight and Size: Drug diffusion is determined by the molecular weight and size, hydrophilicity and lipophilicity of the molecule.

b) Solubility: Dug solubility is a major component in determining the absorption of drugs across biological membranes. Due to the highly aqueous nature of nasal secretions, a drug with good aqueous solubility would show good solubility and good permeability.

c) Lipophilicity: As the compound's lipophilicity increases, its penetration through the nasal mucosa is enhanced.

d) pKa and partition coefficient: Unionized species are absorbed more readily than ionized species, according to the pH partition theory; the same thing is true for nasal absorption. The nasal absorption of drugs and their pKa have a consistent connection.

e) Polymorphism: Drug dissolution and absorption across biological membranes are known to be affected by polymorphism. When developing the dosage form for nasal distribution, this factor should be carefully considered when selecting the right polymorph.

f) Chemical state: The chemical state of the drug when it is administered to the nasal mucosa determines how well it is absorbed.

g) Physical state: The two most important characteristics of powder nasal drug products are particle size and morphology. The drug dissolve in the nostrils with the appropriate characteristics, these two criteria need to be controlled.

4. Formulation of nasal spray: [1,11,16]

Nasal spray drug products are administered through non-pressurized dispensers that provide a metered dose of the active ingredient in spray form. Therapeutically active ingredients, or drug substances, are dissolved or suspended in solutions or mixtures of excipients, such as preservatives, viscosity modifiers, emulsifiers, and buffering agents. The spray pump has metered dose ability. A

nasal spray can be made to deliver hundreds of metered sprays of a drug formulation, or it can be designed for unit dosing. For the consistent distribution of drug formulation, metering and spray producing (orifice, nozzle, jet) pump mechanisms and components are utilized. These can be built from a variety of components with precisely controlled dimensions and composition. The formulation needs energy to disperse as a spray. Nasal sprays can be prepared using either a solution or a suspension.

1) Active Pharmaceutical Ingredient:

An ideal drug candidate should possess the following characteristics:

- Adequate water solubility in a 25–150 ml formulation capacity to deliver the intended dose.
- Superior nasal absorption properties.
- No nasal irritation.
- Quick onset of action.
- Minimal dosage. typically, lower than 25 mg per dose.
- No harmful metabolites in the nose.
- No drug related offensive odors or fragrance.
- Suitable stability attributes.

2) Excipients used in nasal spray formulations: There are various types of excipients used in nasal formulations. The following excipients are typically added and used frequently:

Table no. 1

Sr. No.	Category	Role	Example
1)	Tonicity	Used to adjust the tonicity of the formulation	Sodium chloride, Dextrose
2)	pH	Used to adjust the pH same to physiological conditions and increases drug stability	Sodium hydroxide, hydrochloric acid, sulphuric acid
3)	Inert gas	Used to replace air in the container to reduce oxidation	Nitrogen, hydrogen
4)	Preservatives	To prevent the microbial growth in the formulation occurs due to accidental contamination	Benzalkonium chloride, ethanol, propylene glycol, Benzyl Alcohol, chlorobutanol, Methyl paraben
5)	Buffer	It buffers the formulation at desired pH	Sodium citrate, Sodium Phosphate
6)	Surfactant	Increases wettability, suspend ability and stability of suspension	Polysorbate 80,20
7)	Chelating agent	Forms chelate with ions present in the formulation and increases the stability	Disodium EDTA, citric acid
8)	Suspending agent	Increases viscosity and suspend ability of suspension	CMC, Na CMC
9)	Co-Solvent	Helps to improve solubility	Alcohol, PEG 400, Propylene Glycol
10)	Humectant	Used to keep moisture content in the formulation	Glycerin, propylene glycol

5. Characterization of Nasal Spray: [1,5,16,17]

1) pH: The pH of the formulation should be evaluated, and an appropriate acceptability limit should be set for both liquid nasal sprays. To prevent sneezing, the formulation's pH should be close to that of the human nasal mucosa (5.0–6.5).
2) Osmolality: The osmolality of the formulation should be examined and regulated so that the active ingredient is released from the formulation at the desired rate. The ideal range for osmolality is 300–700 mOsmol/kg.
3) Viscosity: A formulation having higher viscosity increases the contact time between the drug and the nasal mucosa and improves its absorption.
4) Impurities and degradation products: The amounts of contaminants and degradation products should be evaluated using an analytical process that has been validated. The relevant ICH guidelines need to be followed.
5) Preservatives and Stabilizing Excipient: Preservatives, antioxidants, chelating agents, and other stabilizing excipients (benzalkonium chloride, phenylethyl alcohol, edetate, etc.)

should all have particular assays and acceptance criteria if they are used in the formulation.

6) Pump Delivery: It is necessary to conduct a test for assessing pump-to-pump reproducibility in terms of drug product performance and to analyze pump delivery.
7) Spray Content Uniformity (SCU): The spray that emerges from the nasal actuator must be evaluated to determine the amount of drug substance in each spray from the start of the container to the finish.
8) Spray Pattern and Plume Geometry: The evaluation of the pump's performance requires the characterization of the spray pattern and plume geometry. The size and shape of the nozzle, the pump's design, the metering chamber's capacity, and the formulation's properties are some of the variables that can affect the spray pattern and plume geometry.
9) Droplet Size Distribution: A nasal spray's droplet size distribution is an important parameter as it impacts the drugs in vivo deposition in the nasal cavity and must be measured. The recommended size of a droplet can range from 30 to 120 μm.
10) Particle Size Distribution: Estimation of particle size distribution of the drug in the formulation should be included in the specification for nasal spray suspensions.

6. Advantages: [1,11]

- Avoids first pass hepatic and intestinal metabolism and enter the systemic blood circulation directly.
- Quick drug absorption and fast onset of action.
- Improved bioavailability.
- Good drug penetration via the nasal mucosa, particularly for lipophilic low molecular weight drugs.
- Blood brain barrier penetration is easy for lipophilic drugs.
- Improved nasal bioavailability for smaller drug molecules.
- Non-invasiveness, essentially painless, needle-free administration, convenience in medication delivery, and a well-tolerable profile.
- Absorption rate similar to intravenous medicine.
- Easily Accessible.
- By this route, self-medication is possible.
- Beneficial for delivering drugs both locally and systemically.
- Reduces the chance of an overdose.

7. Limitations: [1,11]

- The dosage is limited due to the comparatively small area where the drug can be absorbed.
- Drug absorption has a limited amount of time.
- The histological toxicity of the absorption enhancers employed to improve the nasal drug delivery method is still unknown.
- Nasal irritation
- In high concentrations, several surfactants that are utilized as chemical enhancers have the potential to dissolve or even disturb membranes.
- Adversely affected by pathological conditions.

8. CONCLUSION

Nasal spray drug products have active components that are suspended or dissolved in excipient mixtures or solutions. in non-pressurized dispensers that spray an active ingredient at a dose that is measured. Spray pattern, droplet size distribution, and spray content uniformity are critical characterization tests for nasal sprays that depend on formulation and device features. Numerous factors, such as biological and physiological parameters, as well as the physicochemical properties of drugs and formulations, might influence the distribution of drugs through the nasal cavity. Treatment and immunization administered parenterally and orally can only have a systemic impact. By dispelling the virus at the point of entrance, nasal sprays can dramatically reduce the spread of the infection to deeper regions. Device and formulation technologies can enhance drug deposition to get the optimal therapeutic impact for nasal sprays. Drug delivery systems designed to deliver the drug via intra-nasal routes hold greater promise of therapeutic efficacy at a fraction of the cost of other novel drug delivery systems and may be the choice of the future scientists and patients.

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