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Journal of Advanced Scientific Research

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ISSN
0976-9595
Review Article

A REVIEW ON CHALLENGES IN DEVELOPING NASAL SPRAYS

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Received: 06-05-2022; Accepted: 19-08-2022; Published: 30-09-2022

 https://doi.org/10.55218/JASR.202213802

ABSTRACT

The aim of this review is to provide information regarding significant aspects and challenges in developing of nasal sprays. This article outlined the relevant aspects of nasal anatomy, physiology & biological, physicochemical and pharmaceutical factors that must be considered during formulation development of nasal sprays. Nasal drug delivery system is the most preferable route than other routes of administration as it gives rapid onset of action. It is considered as a convenient and reliable route for local and also for systemic administration of drugs. The main highlights of this review includes types, advantages, disadvantages, mechanisms of drug absorption, factors of nasal drug absorption, formulation, methods of manufacturing and filling of nasal sprays, evaluation, characterization and applications.

Keywords: Nasal sprays, Nasal drug delivery system, Nasal route, Nasal absorption enhancers.

1. INTRODUCTION

Nasal sprays are pharmaceutical dosage forms in which drug substance is dispensed as a fine spray from a container into nostril. It is a liquid medication that is inhaled as a fine spray. The nasal cavity is one of the easily accessible route, which is generally well tolerated.

Intranasal drug delivery is considered to be an alternative to oral and parenteral routes. The nasal route of drug delivery can be used for both local and systemic drug delivery. It is usually used to treat conditions related to the nasal cavity, such as congestion, rhinitis, sinusitis and related allergic conditions.

Administration of drug through nasal route is referred as nasal drug delivery system. Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption [1, 2].

2. ANATOMY AND PHYSIOLOGY OF NASAL CAVITY

The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while anterior part of the nasal cavity is the nasal vestibule which opens to the face through the nostril. The nasal cavity consists of three main regions; nasal vestibule, olfactory region and respiratory region. The surface area of nose is about 150cm^2. This folded structure consists of three turbinates; the superior, the median and the inferior. The nasal cavity is covered with a mucous membrane and is divided into two areas; nonolfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, whereas respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport. The goblet cells present in the mucus membrane covers the nasal turbinate and the atrium and it secretes the mucus [3, 4].

The mucus secretion is composed of about 95% water, 2 % mucin, 1% salts, 1% of other proteins such as albumin, immunoglobulins, lysozyme and lactoferrin, and 1% lipids. The mucus secretion gives immune protection against inhaled bacteria and viruses. It also performs a number of physiological functions.

Breathing and olfaction are the major function of human nose. Nasal cavity has mucus layer and hairs which are helpful in filtration of particles trapped in inhaled air. Mucociliary clearance is a function of nose [5].

3. TYPES OF NASAL DRUG DELIVERY SYSTEMS

3.1. Nasal Drops and Sprays

Nasal drops are most simple and convenient systems developed for nasal delivery. It is reported that nasal drops deposit human serum albumin in nostrils more

efficiently than nasal sprays. The main disadvantage of nasal drops is lack of dose precision. Both solution and suspension forms can be formulated into nasal sprays. Due to availability of metered dose pumps and actuators, nasal spray can deliver an exact dose of 25 to 200µl. Choice of pumps and actuators depends on particle size, morphology of drug and viscosity of formulation [6].

3.2. Nasal Gels

Nasal gels are high-viscosity thickened solutions or suspensions. The advantages of a nasal gel is the reduction of postnasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation using soothing/emollient excipients, and target delivery to mucosa for better absorption [7].

3.3. Nasal Powder

The dosage form may be developed if solution and suspension dosage forms cannot be developed due to lack of drug stability. The advantages are absence of preservatives, local application of drug is possible [8].

3.4. Advantages of Nasal Drug Delivery Systems

- Drugs unabsorbed orally can be delivered to the systemic circulation by means of nasal drug delivery.
- Hepatic first pass metabolism is avoided.
- Easy accessibility.
- Self-medication is possible.
- Improved patient compliance.
- Drug degradation observed in the gastrointestinal tract is absent.
- Improved bioavailability.
- Rapid drug absorption.
- Quick onset of action can be achieved.
- The nasal bioavailability for smaller drug molecules is good.
- Drug possessing poor stability in GIT fluids are given by nasal route [9].

3.5. Disadvantages of Nasal Drug Delivery Systems

- Nasal cavity provides smaller absorption surface area when compared to GIT.
- Relatively inconvenient to patient when compared to oral delivery system since there is a possibility of irritation.
- There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
- There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of improper technique of administration.
- Certain surfactants used as chemical enhancers may disrupt and even dissolve the membrane in high concentration.
- The nasal route of delivery is not applicable to all drugs. Absorption of polar drugs and some macromolecules are insufficient due to poor membrane permeability, rapid clearance, and enzymatic degradation into the nasal cavity.
- Nasal drug administration is limited, however, to very small volumes (25-200µl), and thus only applicable to potent drugs with high water solubility.
- The active ingredient must have a molecular weight <1 kDa to be absorbed.
- Nasal route of drug administration is not suitable for drugs that are irritating or injurious to the nasal mucosa.
- Diseases conditions of the nose may result in impaired absorption [10, 11].

4. MECHANISM OF DRUG ABSORPTION THROUGH NOSE

The absorbed drug from the nasal cavity passes through the mucus layer. It is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs find difficulty to cross it.

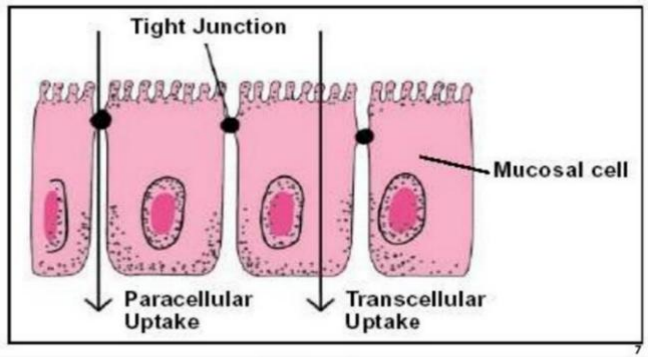
Mechanism of drug absorption through nose occurs in two mechanisms:

4.1. Paracellular transport

It is defined as the transfer of substances across epithelium by passing through intercellular spaces between the cells. It is an aqueous route of transport with slow and passive process [12].

4.2. Transcellular transport

It is defined as transport of solutes by a cell through a cell. It involves transport through lipoidal membrane. It is an active transport via carrier mediated means [13].



Mechanism of absorption

5. BARRIERS TO NASAL ABSORPTION

5.1. Low bioavailability

Lipophilic drugs are generally well absorbed from the nasal cavity compared to polar drugs. It is due to low membrane permeability.

5.2. Low membrane transport

Rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism. This is especially the case for drugs that are not easily absorbed across the nasal membrane [13].

5.3. Enzymatic Degradation

Low transport of especially peptides and proteins across the nasal membrane is the possibility of an enzymatic degradation of the molecule either within the lumen of the nasal cavity or during passage across the epithelial barrier by exopeptidase and endopeptidase [14].

6. FORMULATION OF NASAL SPRAYS

Nasal spray drug products contain therapeutically active ingredients (drug substances) dissolved or suspended in solutions or mixtures of excipients (e.g., preservatives, viscosity modifiers, emulsifiers, buffering agents) in no pressurized dispensers that deliver a spray containing a metered dose of the active ingredient. The dose can be metered by the spray pump. A nasal spray unit can be designed for unit dosing or can discharge up to several hundred metered sprays of formulation containing the drug substance. Nasal sprays are applied to the nasal cavity for local and/or systemic effects. Although similar in many features to other drug products, some aspects of nasal sprays may be unique (e.g., formulation, container closure system, manufacturing, stability, and drug product). Metering and spray producing (e.g., orifice, nozzle, jet) pump mechanisms and components are used for reproducible delivery of drug formulation, and these can be constructed of many parts of different design that are precisely controlled in terms of dimensions and composition. Energy is required for dispersion of the formulation as a spray. This is typically accomplished by forcing the formulation through the nasal actuator and its orifice. The formulation and the container closure system (container, closure, pump, and any protective packaging) collectively constitute the drug product. The design of the container closure system affects the dosing performance of the drug product. Both solution and suspension formulations can be formulated into nasal sprays [12, 15].

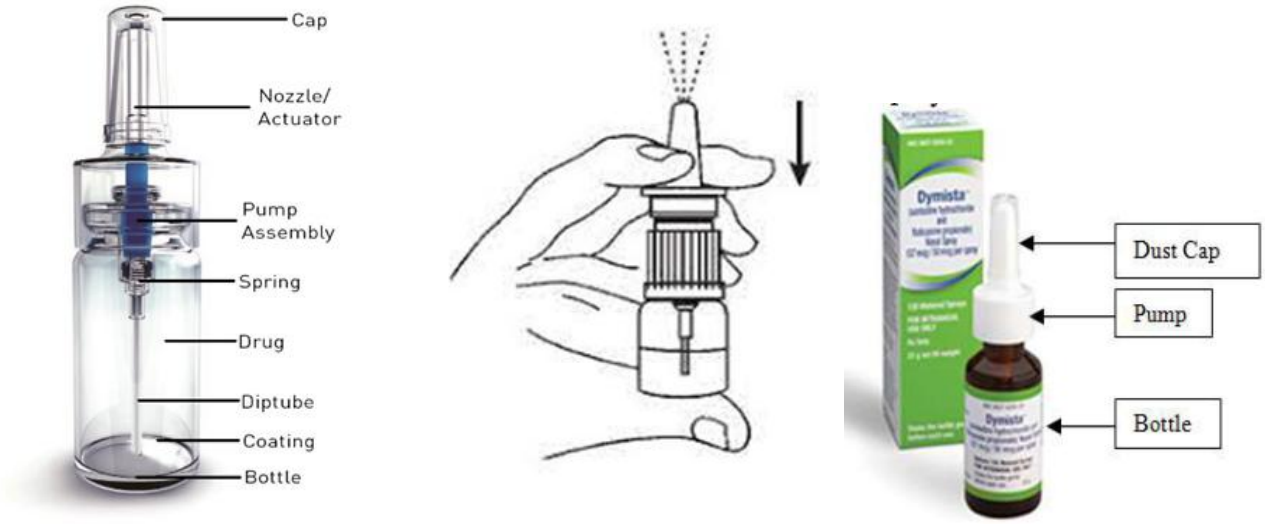


Fig. 1: Nasal sprays

Table 1: Commonly utilized Excipients

Category	Role	Example	IIG limits for nasal sprays (%w/w)
Tonicity Adjusting agent	Used to adjust tonicity of formulation	NaCl, Anhydrous Dextrose	0.9 0.5
pH Adjustment	Used to adjust pH same to physiological conditions and maximize drug stability	Sodium hydroxide, Sulphuric acid, Hydrochloric acid	0.004 0.4
Purging	Used to reduce oxidation	Butylated hydroxyl toluene Butylated hydroxyl anisole	0.01 0.0002
Antimicrobial Preservative	To avoid microbial growth in the formulation	Benzyl alcohol Benzalkonium chloride Chlorobutanol Propylene glycol	0.0366 0.119 0.5 20
Buffer component	It gives buffer capacity to formulation at desired pH	Anhydrous trisodium citrate	0.0006
Surfactant	Increases suspendability and stability of suspension	PEG 400 PEG 3500	20 1.5
Cation chelating agent	Forms chelate with ions present in formulation and increases stability	Disodium EDTA	0.5
Suspending agents	Increase viscosity and suspendability of suspension	CMC-Na	0.15
Co-solvent	Helps to improve solubility	Alcohol PEG 400 Propylene glycol	2 20 20
Humectant	Used to maintain humidification in the formulation	Glycerin	0.233

7. CHALLENGES OF NASAL DRUG DELIVERY

7.1. Nasal geometry and site of drug deposition

Nasal drug delivery system is more effective for local action, systemic action, and central nervous system action, at lower doses with minimum side effects. However, delivering drug to the specific regions is challenging. As mentioned earlier, these challenges arise due to winding and narrow geometry of the nasal airways filter most droplets into the anterior part of the cavity as most of them are located in the posterior nasal cavity. To overcome these challenges new devices are in development to target drugs to these regions. With the help of these new devices, we can overcome challenges and can deposit drug within specific areas of the nasal cavity.

7.2. Mucociliary clearance

It plays an important role in therapeutic activity of drug in posterior nasal cavity so that absorption occurs more quickly. Use of absorption enhancers and muco-adhesives increase residence time.

Preservatives are used to prevent microbial growth and microbial contamination in solution and suspension nasal formulations which resulted in adverse effects. So to overcome the adverse effects caused by use of preservatives lead to the development of preservative free formulations by using various novel approaches, preservative free devices and sterile manufacturing techniques.

Other challenges are as follows:

- Drug diffusion through mucus layer and transport across respiratory epithelial membrane.
- Potential degradation by extracellular and intracellular enzyme systems.

Majority of nasal formulations are prepared by use of active pharmaceutical ingredient (API) and various excipients like preservatives, suspending agents, emulsifiers, buffering agents etc. Microbial contamination may occur during manufacture such as handling process during manufacturing, use of contaminated excipients or when used by the patients [16, 17].

8. EVALUATION OF NASAL FORMULATIONS

8.1. *In vitro* diffusion studies

The nasal diffusion cell is fabricated in glass. The water-jacketed recipient chamber has total capacity of 60ml

and a flanged top of about 3mm; the lid has 3 opening, each for sampling, thermometer, and a donor tube chamber. The 10 cm long donor chamber tube has internal diameter of 1.13 cm. The nasal mucosa of sheep was separated from sub layer bony tissues and stoned in distilled water containing few drops of gentamycin injection [18].

After the complete removal of blood from mucosal surface, it is attached to donor chamber tube. The donor chamber tube is placed such a way that it just touches the diffusion medium in recipient chamber. At predetermined intervals, samples (0.5 ml) from recipient chamber are withdrawn and transferred to amber colored ampoules. The samples withdrawn are suitably replaced. The samples are estimated for drug content by suitable analytical technique. Throughout the experiment the temperature is maintained at 37°C [19].

8.2. *In vivo* studies

Various animal compartment models are used for *in vivo* evaluation studies. The most convenient model is anesthetized rat model. For most non-peptic drugs results obtained in rats can accurately reflect absorption profiles in humans. Some other animal models are rabbit model, dog model, monkey model, etc. [20].

8.3. Characterization of Nasal Spray

8.3.1. pH

For both, solution and suspension nasal sprays, the pH of the formulation should be tested and an appropriate acceptance criteria is established. In healthy human volunteers, overall range of pH of the anterior part of the nose was 5.17 to 8.13 while that of the posterior part was 5.20 to 8.00, indicating that an average baseline human nasal pH is approximately 6.3. Thus the stability can be achieved by proper selection of pH of formulation. However, the pH of formulation should be near to human nasal mucosa (5.0-6.5) to prevent the sneezing [21].

8.3.2. Osmolality

For formulations containing an agent to control the tonicity, the osmolality of the formulation should be tested and controlled at release. The data from animal models has shown increased bioavailability for salmon calcitonin from nasal spray formulations with an osmolality of 100 or 600mOsmol/Kg compared to isotonic formulations. Other studies have shown that hypotonic nasal spray formulations improved drug permeability through the nasal mucosa. Some existing marketed products have reported osmolality in the range of 300-700mOsmol/Kg.

8.3.3. Viscosity

For formulations containing an agent contributing to the viscosity, this parameter should be tested and controlled at release and on stability. The contact time between the drug and the nasal mucosa is increased by higher viscosity of formulation thereby increasing the time for permeation. Also high viscosity of formulations interferes with normal ciliary beating or MCC and, thus, increases the permeability of drugs [22].

8.3.4. Spray Content Uniformity (SCU)

The spray discharged from the nasal actuator should be thoroughly analyzed for the drug substance content of multiple sprays from beginning to the end of an individual container, among containers, and among batches of drug product. This test should provide an overall performance evaluation of a batch, assessing the formulation, the manufacturing process, and the pump. This test is designed to demonstrate the uniformity of medication per spray, consistent with the label claim, discharged from the nasal actuator, of an appropriate number (n = 10 from beginning and n = 10 from end) of containers from a batch. The primary purpose is to ensure SCU within the same container and among multiple containers of a batch [23].

8.3.5. Spray Pattern and Plume Geometry

Characterization of spray pattern and plume geometry are important for evaluating the performance of the pump. Various factors can affect the spray pattern and plume geometry, including the size and shape of the nozzle, the design of the pump, the size of the metering chamber, and the characteristics of the formulation. Plume geometry testing requires images taken from a sideward view of the emitted spray parallel to the axis of the plume, whereas for the evaluation of the spray pattern, an image of an axial cross-section of the plume at a defined distance to the nozzle is compulsory. The evaluation of plume includes plume angle, Width and height. The spray pattern is evaluated for maximum diameter (Dmax) and minimum diameter (Dmin), orality ratio (Dmax/Dmin) measurements should be performed at two distances from the actuator tip, and the selected distances should be at least 3 cm apart within the range of 3 to 7 cm [24].

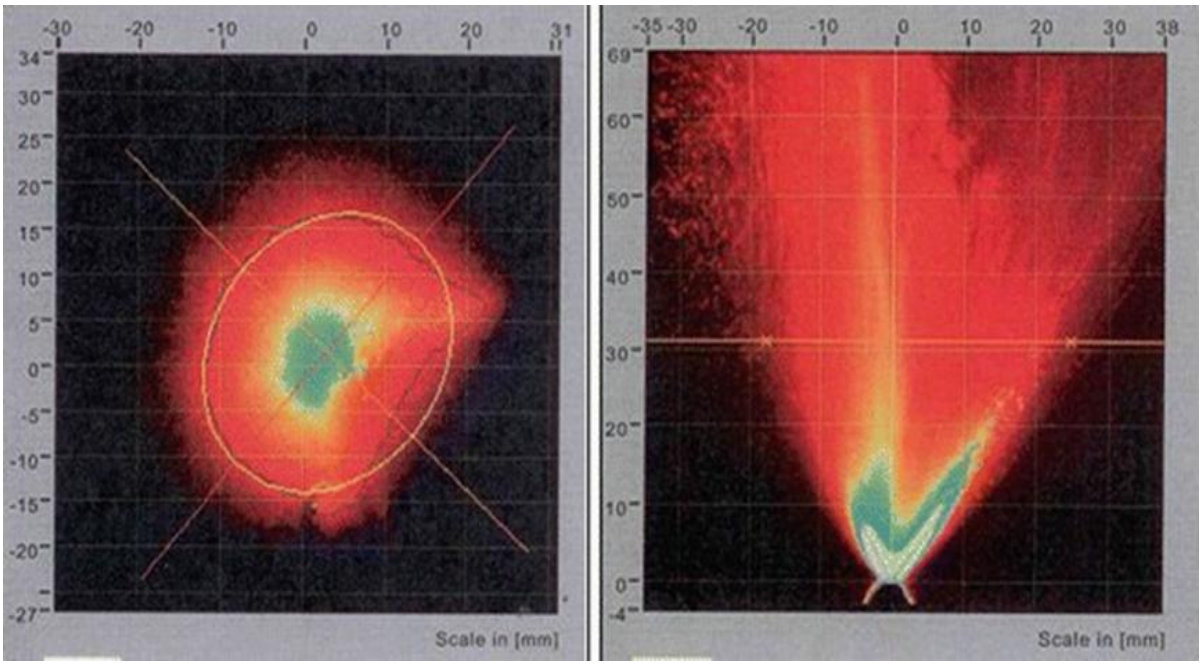


Fig. 2: Plume geometry and Spray pattern

9. APPLICATIONS

9.1. Delivery of non-peptide pharmaceuticals:

Low molecular weight (below 1000 Daltons) small nonpeptide lipophilic drugs are well absorbed through the nasal mucosa even in absence of permeation enhancer. Nasal membrane containing epithelium is highly vascularized and it contains large surface area it is readily accessible for drug absorption becauseof presence of nasal turbinates. Drugs with extensive pre-systemic metabolism, such as progesterone, estradiol, propranolol, nitroglycerin, sodium chromoglyate can be rapidly absorbed through the nasal mucosa with a systemic bioavailability.

9.2. Delivery of peptide-based pharmaceuticals

Peptides & proteins have a generally low oral bioavailability because of their physic-chemical instability and susceptibility to hepato gastrointestinal first-pass elimination. Examples are insulin, calcitonin, pituitary hormones etc. These peptides and proteins are hydrophilic polar molecules of relatively high molecular weight, are poorly absorbed across biological membranes with bioavailability obtained in the region of 1-2% concentrations when administered as simple solutions. To overcome this problem mainly we are using the absorption enhancers like surfactants, glycosides, cyclodextrin and glycols to increase the bioavailability. Nasal route is proving to be the best route for such biotechnological products [25].

9.3. Delivery of Drugs to Brain through Nasal Cavity

This delivery system is beneficial in conditions like Parkinson's disease, Alzheimer's disease or pain because it requires rapid and specific targeting of drugs to the brain. The olfactory region located at the upper parts of the nasal passages offers the potential for certain compounds to circumvent the blood-brain barrier and enter into the brain. Studies in humans, with proteins such as AVP, CCK analog, MSH/ACTH and insulin have revealed that they are delivered directly to the brain from the nasal cavity [26].

9.4. Delivery of Vaccines through Nasal Route

Nasal delivery of vaccines has been reported to not only produce systemic immune response, but also local immune response in the nasal lining, providing additional barrier of protection. Delivering the vaccine to the nasal cavity itself stimulates the production of local secretory IgA antibodies as well as IgG, providing an additional first line of defense, which helps to eliminate the pathogens.

9.5. Delivery of diagnostic drugs

Nasal drug delivery system can be used for the diagnosis of various diseases and disorders in the body. Intranasal route is better for systemic release of medicament into blood circulation, so can get quick results with less toxicity. Phenol sulfonphthalein is a diagnostic agent

used to diagnose the kidney function of the patients [27].

10. CONCLUSION

This is to conclude that nasal route is easily accessible for self-administration without help of health professionals. It is the best route for administration of drugs which degrade due to first pass metabolism. It provides rapid onset of action, reduced risk of overdose and improved patient compliance.

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