Formulation and Product Development of Nasal Spray: An Overview

Santosh Thorat
Lupin Research Park, Hinjewadi, Pune, 411057, India

*Corresponding author
Santosh Thorat
Email: santoshthorat345@gmail.com

Abstract: The intranasal delivery is preferable route for administration of the drug for local, systemic as well as central nervous system drug delivery. Advantages of nasal spray dosage form such as it is cost-effective, easy to use/carry and self-administrable, it has high patient compliance make this dosage form growing opportunity for nasal drug delivery. This article outlined the relevant aspects of nasal anatomy, physiology and histology, and the biological, physicochemical and pharmaceutical factors that must be considered during the formulation development of nasal spray. It is intuitively expected that this review will help to understand nasal formulation and its in-vitro characteristics.

Keywords: Nasal Spray, Nasal drug delivery system, formulation and in-vitro characterization.

INTRODUCTION:

Intranasal drug delivery is recognized to be a useful and reliable alternative to oral and parenteral routes. The nasal route of drug delivery can be used for both local and systemic drug delivery. For instance, localized nasal drug delivery is usually used to treat conditions related to the nasal cavity, such as congestion, rhinitis, sinusitis and related allergic conditions. A diverse range of drugs including corticosteroids, anti-histamines, anti-cholinergic and vasoconstrictors can be administered locally. In recent years, achieving a systemic drug action using the nose as the entry portal into the body has received more attention. Also, the nasal delivery seems to be a favorable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS)-active compounds. It has also been considered to the administration of vaccines.

Now a day’s multiple types of formulation are used to administer drug by nasal rout, which includes nasal spray, nasal drop, nasal powder, nasal gels & nasal insert etc. Administration of drugs through the nose in the spray dosage form is a non-invasive method that gives rapid onset of drug action. Because the nasals spray dosage form is cost-effective, easy to use/carry and self-administrable, it has high patient compliance. Therefore, nasal drug delivery has become a popular route of drug administration and has strong growth opportunity [1].

Only relatively recently have specially-designed devices emerged that can target the delivery of sprays or powders to the olfactory region of the nose, thereby enabling delivery of the drug directly to the central nervous system.

The present review outlines anatomical, physiological and histological features of nasal cavity and the major factors affecting nasal drug delivery, the properties of drugs and formulation characteristics that determine decisively the pharmacokinetics of nasal preparations. Along with this article examines nasal spray formulation parameters, excipients, characterization and their influence on key in-vitro tests.

Advantages of Nasal Drug Delivery System [2]:

1. Intranasal administration offers several practical advantages from the viewpoint of patients (non-invasiveness, essentially painless, ease drug delivery and favorable tolerability profile)
2. Rapid drug absorption.
3. Quick onset of action.
4. Hepatic first – pass metabolism is absent.
5. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
Limitations:
1. Dose is limited because of relatively small area available for the absorption of drug.
2. Time available for drug absorption is limited.
3. Diseased condition of nose impairs drug absorption.
4. The absorption enhancers used to improve nasal drug delivery system may have histological toxicity which is not yet clearly established.
5. Absorption surface area is less when compared to GIT.
6. Nasal irritation
7. Certain surfactants used as chemical enhancers may disrupt and even dissolve Membrane in high concentration.

Nasal Anatomy and Physiology [3, 4]:
Nasal cavity is lined with mucus layer and hairs which are involved in those functions, trapping inhaled particles and pathogens. Moreover, resonance of produced sounds, mucociliary clearance MMC, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures. The human nasal cavity has a total volume of 15-20 mL and a total surface area of approximately 150 cm$^2$. The nasal halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics (Figure 1; Table 1).

1) Nasal vestibule
In this area of nasal cavity, there are nasal hairs, also called vibrissae, which filter the inhaled particles. Nasal vestibular characteristics are desirable to afford high resistance against toxic environmental substances but, at the same time, the absorption of substances including drugs becomes very difficult in this region.

2) Atrium
Atrium is the intermediate area between nasal vestibule and respiratory region. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by pseudostratified columnar cells presenting microvilli.

3) Respiratory region
It is divided in superior, middle and inferior turbinates which are projected from the lateral wall. These specialized structures are responsible for humidification and temperature regulation of inhaled air. Between them there are spaces, called meatus, which are passageways where airflow is created to assure a close contact of the inhaled air with the respiratory mucosal surface. The inferior and middle meatus receive nasolacrimal ducts and paranasal sinuses which are air-filled pockets located inside the bones of the face and around the nasal cavity. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. Nasal mucus is indispensable for several physiological functions, such as humidification and warming of the inhaled air, and also offers physical and enzymatic protection of the nasal epithelium against several foreign compounds, including drugs. The presence of mucin in the nasal mucus layer is crucial because it may trap large molecular weight drugs, such as peptides and proteins. Beneath of it, there is the lamina propria which is richly supplied with blood vessels, including many very permeable fenestrated capillaries, nerves, glands and immune cells. The last ones produce immunoglobulin antibodies that confer immunological protection against bacteria and virus.

Fig-1: Anatomy and histology of human nasal cavity.

4) Olfactory region
The olfactory region is located in the roof of the nasal cavity and extends a short way down the septum and lateral wall. Its neuroepithelium is the only part of the CNS that is directly exposed to the external environment. Similarly to the respiratory epithelium, the olfactory one is also pseudostratified but contains specialized olfactory receptor cells important for smell perception.

**Table 1: Human nasal epithelium characteristics**

<table>
<thead>
<tr>
<th>Nasal Sections</th>
<th>Epithelial Characteristics</th>
<th>Surface Area</th>
<th>Vascularization</th>
<th>Permeability</th>
</tr>
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<tbody>
<tr>
<td>Vestibule</td>
<td>Stratified squamous and keratinized epithelial cells with nasal hairs / Support and protection</td>
<td>≈ 0.6 cm²</td>
<td>Low</td>
<td>Poor</td>
</tr>
<tr>
<td>Atrium</td>
<td>Stratified squamous cells / Support Pseudostratified cells / Support</td>
<td>NF</td>
<td>Low</td>
<td>Reduced</td>
</tr>
<tr>
<td>Respiratory Region</td>
<td>Columnar non ciliated cells / Support - Columnar ciliated cells / Support and muciliary clearance - Globet cells / Mucus secretion - Basal cells / Progenitors of other cell types</td>
<td>≈ 130 cm²</td>
<td>Very high</td>
<td>Good</td>
</tr>
<tr>
<td>Olfactory region</td>
<td>Sustentacular cells / Support and synthetic - Olfactory receptor cells / Olfaction Perception - Basal cells / Progenitors of other cell Types</td>
<td>≈ 15 cm²</td>
<td>High</td>
<td>Direct access to CNS</td>
</tr>
</tbody>
</table>

**Different factors affecting nasal drug absorption [4-5]**

Various factors affect bioavailability of nasally administered drugs as follows:

A) **Biological factors**

1) Structural features: There are five different sections of nasal cavity: nasal vestibule, atrium, respiratory area, olfactory region and the nasopharynx. These structures and the type of cells, density and number of cells present in that region influence the permeability. Absorption enhancers used in combination with drugs increase the permeation of compounds.

2) Biochemical changes: Enzymatic barrier to the delivery of drugs is nasal mucosa because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes, peptidases and proteases. Protease and peptidase were responsible for the presystemic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin. To overcome these degradations use of protease and peptidase inhibitors such as bacitracin, amastatin, boroleucin and puromycin can be used.

B) **Physiological factors**

1) Blood supply and neuronal regulation

Nasal mucosa is highly permeable site. High blood supply due to parasympathetic stimulation gives congestion and low blood supply due to sympathetic stimulation gives relaxation, regulate the rise and fall in the amounts of drug permeated, respectively. Based on the above observations, we can conclude that the increased permeability of a compound is due to parasympathetic stimulation.

2) Nasal secretions

Nasal secretions are produced by anterior serous and seromucus glands. The permeability of drug through the nasal mucosa is affected by:

- **Viscosity of nasal secretion:** The viscous surface layer will inhibit the ciliary beating if the sol layer of mucus is too thin and mucociliary clearance is impaired if sol layer is too thick, because contact with cilia is lost. Permeation of the drug is affected due to impairment of mucociliary clearance by altering the time of contact of drug and mucosa.
- **Solubility of drug in nasal secretions:** For permeation of drug solubilisation is necessary. A drug needs to have appropriate physicochemical characteristics for dissolution in nasal secretions.
- **pH of nasal cavity variation:** In adults the pH is observed between 5.5–6.5 and in infants 5.0–7.0. Permeation of drug is greater if the nasal pH is lower than pKa of drug because under such conditions the penetrant molecules exist as unionized species.

3) Mucociliary clearance (MCC) and ciliary beating

Whenever a substance is nasally administered, it is cleared from the nasal cavity in ~21 min by MCC because mucociliary clearance is the normal defense mechanism of the nasal cavity which clears substances adhering to nasal mucosa and cleared in GIT by draining into nasopharynx. Drug permeation is enhanced by increasing contact time between drug and mucus membrane because reduced MMC.
4) Pathological conditions:
Mucociliary disfunctioning, hypo or hypersecretions, irritation of the nasal mucosa occurs due to diseases such as the common cold, rhinitis, atrophic rhinitis and nasal polyposis, and drug permeation is affected by this.

5) Environmental conditions:
Moderate reduction in the rate of MCC occurs at the temperature of 24°C, it has been predicted that a linear increase in ciliary beat frequency occurs with increase in temperature.

6) Membrane permeability:
Absorption of the drug through the nasal route is affected by membrane permeability which is most important factor. The large molecular weight drugs and water soluble drugs like peptides and proteins have low membrane permeability hence absorbed through endocytic transport in fewer amounts.

C) Physicochemical properties of drug:
1) Molecular weight and size: Drug permeation is determined by molecular weight, molecular size, hydrophilicity and lipophilicity of the compound. For compounds 1 kDa, bioavailability can be directly predicted from knowledge of MW. In general, the bioavailability of these large molecules ranges from 0.5% to 5%. Physicochemical properties of the drug don’t significantly affect permeation of drug LT 300 Da, which will mostly permeate through aqueous channels of the membrane. By contrast, for compounds with MW 300 Da rate of permeation is highly sensitive.

2) Solubility: Major factor in determining absorption of drug through biological membranes is drug solubility. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Lipophilic drugs have less solubility in the aqueous secretions. Water soluble drugs are absorbed by passive diffusion and lipophilic drugs via active transport depending on their solubility.

3) Lipophilicity: The permeation of the compound normally increases through nasal mucosa with increase in lipophilicity. It appears that nasal mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes although they have some hydrophilic characteristics. Systemic bioavailability of many drugs is decreased due to excess hydrophilicity in such cases prodrug approach is beneficial.

4) pKa and partition coefficient: As per the pH partition theory, unionized species are absorbed better compared with ionized species and the same fact is true in the case of nasal absorption. There is constant relationship between pKa and nasal absorption of these drugs. With an increase in lipophilicity or the partition coefficient of the drugs its concentration in biological tissues increases. The absorption rate of aminopyrine increased with the increase in pH and was found to fit well to the theoretical profile. Major factor governing nasal absorption is partition coefficient.

5) Polymorphism: Polymorphism is the important parameter in the nasal drug product development which is administered in particulate form. Polymorphism is known to affect dissolution of drugs and their absorption through biological membranes is affected by polymorphism. This factor should be carefully considered in the dosage form development for the nasal delivery.

6) Chemical state of drug: Absorption of the drug is determined by the chemical form of the drug in which it is presented to nasal mucosa. Chemically alter a drug molecule by adding a bio-cleavable lipophilic moiety is the alternative for improving absorption of the drug which is not having desired absorption properties. The prodrug approach provides many additional challenges which need to be overcome in the drug product developmental process. The toxicity of the prodrug itself needs to be fully evaluated.

7) Physical state of drug:
Particle size and morphology of drug are two main important properties for particulate nasal drug Products. These both parameters should be controlled to obtain suitable drug dissolution properties in the nostrils. Too fine particles below 5 microns should be avoided because it may get inhaled in lungs. Generally, particles in the 5–10 micron range are deposited in the nostrils.

D) Physicochemical properties of formulation:
1) Physical form of formulation:
Liquid formulations are less effective than powder form in delivering insulin in rabbits. Less efficient systemic nasal drug delivery observed with more viscous formulation. Viscous formulations may help in minimizing nasal drip.

2) pH: extent of drug ionization is determined by pH partition hypothesis hence it is related to formulation pH. Nasal formulation should be adjusted to appropriate pH to avoid irritation, to obtain efficient absorption and to prevent growth of pathogenic bacteria. Ideal formulation pH should be adjusted between 4.5 and 6.5.

3) Osmolarity: Formulation tonicity substantially affect the nasal mucosa generally, an isotonic formulation is preferred.

**Formulation of nasal spray [6]:**
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 nonpressurized 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.

2) Excipients used in nasal spray formulations[7]
There are various types of excipients used in nasal formulations. Commonly used and frequently added excipients are as follows:

a) Buffers: Nasal secretions may alter the pH of the administrated dose which can affect the concentration of un-ionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ. Examples of buffer used in nasal spray sodium phosphate, Sodium citrate, citric acid.

b) Solubilizers: Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. Conventional solvents or cosolvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol (saturated polyglycolyzed C8-C10 glyceride) can be used to enhance the solubility of drugs. Other compounds can be used like, the use of surfactants or cyclodextrins such as HP–Cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers. In these cases, their impact on nasal irritancy should be considered.

c) Preservatives: Most nasal formulations are aqueous based so needs preservatives to prevent microbial growth. Parabens, phenyl ethyl alcohol, benzalkonium chloride, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations.

d) Antioxidants: A small quantity of antioxidants may be required to prevent drug oxidation. Commonly used antioxidants are sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite and tocopherol. Usually, antioxidants do not affect drug absorption or cause nasal irritation.

e) Humectants Because of allergic and chronic diseases there can be crusts and drying of mucous membrane. Certain preservatives/antioxidants are also likely to cause nasal irritation especially when used in higher quantities. Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel-based nasal products. Humectants avoid nasal irritation and do not affect drug absorption or cause nasal irritation.

f) Surfactants Surfactant incorporation into nasal dosage forms can modify the permeability of nasal membranes, which may facilitate the nasal absorption of drug. It also

1) Active Pharmaceutical Ingredient
An ideal nasal drug candidate should possess the following attributes:

- Appropriate aqueous solubility to provide the desired dose in a 25–150 ml volume of formulation.
- Appropriate nasal absorption properties.
- No nasal irritation from the drug.
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
- Low dose. Generally, below 25 mg per dose.
- No toxic nasal metabolites.
- No offensive odors/aroma associated with the drug.
- Suitable stability characteristics.

Fig-2: Nasal spray (Dymista™)
increase stability of suspension. Common examples include Polysorbet.

**g) Bioadhesive polymers** Compound that is capable of interacting with biological material through interfacial forces and being retained on such material for prolonged periods of time is called as bioadhesive polymer. They are also called as mucoadhesive if biological material is mucus membrane. The bioadhesive force of a polymer material is dependent on the nature of the polymer, the surrounding medium (pH), swelling and physiological factors (mucin turnover, disease state). From a safety (nasal irritancy) point of view use of a combination of carriers is often recommended.

**h) Penetration enhancer** Chemical penetration enhancers are widely used in the nasal drug delivery.

<table>
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<tr>
<th>Table 2: Commonly utilized excipients</th>
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3) **Metered-dose spray pumps**

Metered spray pumps have, since they were introduced some four decades ago, dominated the nasal drug delivery market. The pumps typically deliver 100 μl (25– 200 μl) per spray, and they offer high reproducibility of the emitted dose and plume geometry in in vitro tests. The particle size and plume geometry can vary within certain limits and depend on the properties of the pump, the formulation, the orifice of the actuator, and the force applied. Traditional spray pumps replace the emitted liquid with air, and preservatives are therefore required to prevent contamination. However, driven by the studies suggesting possible negative effects of preservatives, pump manufacturers have developed different spray systems that avoid the need for preservatives. More recently, pumps have been designed with side-actuation and introduced for delivery of fluticasone furoate for the indication of seasonal and perennial allergic rhinitis. The pump was designed with a shorter tip to avoid contact with the sensitive mucosal surfaces. New designs to reduce the need for priming and re-priming, and pumps incorporating pressure point features to improve the dose reproducibility and dose counters and lock-out mechanisms for enhanced dose control and safety are available.

A simple variant of a single-dose spray device (MAD) is offered by LMA (LMA, Salt Lake City, UT, USA. A nosepiece with a spray tip is fitted to a standard syringe. The liquid drug to be delivered is first drawn into the syringe and then the spray tip is fitted onto the syringe.

| Table 3: Nasal drug products for systemic drug delivery in the market |
Characterization of Nasal Spray [6-8]:

1) **pH**
   
   For both solution and suspension nasal sprays, the pH of the formulation should be tested and an appropriate acceptance criterion established. The 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 achieve by proper selection of pH of formulation. However, the pH of formulation should be near on human nasal mucosa (5.0‐6.5) to prevent the sneezing.

2) **Osmolality**
   
   For formulations containing an agent to control the tonicity or for products having a label claim regarding 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 600 mOsmol/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 300-700 mOsmol/Kg.

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 and/or MCC and, thus, increases the permeability of drugs.

4) **Impurities and Degradation Products**

   The levels of impurities and degradation products should be determined by a validated analytical procedure or procedures. Acceptance criteria should be set for individual and total impurities and degradation products. All related impurities appearing at levels of 0.1 percent or greater should be specified according to ICH guideline for impurities.

5) **Preservatives and Stabilizing Excipients Assay**

   If preservatives, antioxidants, chelating agents, or other stabilizing excipients (e.g., benzalkonium chloride, phenylethyl alcohol, edetate) are used in the formulation, there should be a specific assay for these components with associated acceptance criteria. Acceptance criteria for the chemical content of preservatives at the time of product release and through the product shelf life should be included in the drug product specification.

6) **Pump Delivery**
A test to assess pump-to-pump reproducibility in terms of drug product performance and to evaluate the delivery from the pump should be performed. In general, pump spray weight delivery acceptance criteria should control the weight of the individual sprays to within 15 percent of the target weight and their mean weight to within 10 percent of the target weight.

7) 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. For acceptance of a batch the amount of active ingredient per determination is not outside of 80 to 120 percent of label claim for more than 2 of 20 determinations 10 containers, none of the determinations is outside of 75 to 125 percent of the label claim, and the mean for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim. If the above acceptance criteria are not met because 3 to 6 of the 20 determinations are outside of 80 to 120 percent of the label claim, but none are outside of 75 to 125 percent of label claim and the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim, if the above acceptance criteria are not met because 3 to 6 of the 20 determinations are outside of 80 to 120 percent of the label claim, then none of the determinations is outside of 75 to 125 percent of the label claim, and the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim.

8) 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 include plume angle, Width and height. The spray pattern is evaluated for maximum diameter (Dmax) and minimum diameter (Dmin), ovality 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.

9) Droplet Size Distribution

The DSD of a nasal spray is a critical parameter, since it significantly influences the in vivo deposition of the drug in the nasal cavity. The droplet size is hereby mainly influenced by the design and handling, e.g., the actuation parameters, of the device, as well as by the formulation, and the prevalent median droplet size is between 30 and 120 µm. If the droplets are too large (>120 µm), deposition takes place mainly in the anterior parts of the nose, and if the droplets are too small (<10 µm), they can possibly be inhaled and reach the lungs, which should be avoided because of safety reasons. For both suspension and solution nasal sprays, the specifications should include an appropriate control for the droplet size distribution (e.g., 3 to 4 cut-off values) of the delivered plume subsequent to spraying under specified experimental and instrumental conditions. If a laser diffraction method is used, droplet size distribution can be controlled in terms of ranges for the D10, D50, D90, span [(D90-D10)/D50], and percentage of droplets less than 10 µm.

10) Particle Size Distribution

For suspension nasal sprays, the specification should include tests and acceptance criteria for the particle size distribution of the drug substance particles in the formulation. For example, microscopic evaluation can be used and such an examination can provide information and data on the presence of large particles, changes in morphology of the drug substance particles, extent of agglomerates, and crystal growth.

Advances [10-11]

1) Systemic delivery

The intranasal administration of drugs is having advantages as compared to oral and intravascular route, such as fast and extended drug absorption. Examples for systemic delivery include marketed product containing the drug zolmitriptan and sumatriptan for the treatment of migraine and cluster headaches. As well as other drugs like analgesics (morphine), cardiovascular drugs as propranolol and carvedilol, hormones such as levonorgestrel, progesterone and insulin, anti-inflammatory agents as indomethacin and ketorolac, and antiviral drugs (acyclovir).

2) Vaccines
Use for vaccination, especially against respiratory infections, has been extensively evaluated. It is able to enhance the systemic levels of specific immunoglobulin G and nasal secretary immunoglobulin A. Examples of the human efficacy of intranasal vaccines include those against influenza A and B virus, proteosoma-influenza, adenovirus-vectored influenza, group B meningococcal native, attenuated respiratory syncytial virus and parainfluenza 3 virus.

3) Liposomes

Liposomal drug delivery systems present various advantages such as the effective encapsulation of small and large molecules with a wide range of hydrophilicity and pKa values. In fact, they have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration. This has been attributed to the increasing nasal retention of peptides, protection of the entrapped peptides from enzymatic degradation and mucosal membrane disruption. Moreover, liposomal drug delivery systems were also reported as useful for influenza vaccine and non-peptide drugs such as nifedipine.

4) Microsphere

Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery. Furthermore, microspheres may also protect the drug from enzymatic metabolism and sustain drug release, prolonging its effect. Gelatin microspheres as a nasal drug delivery system for insulinshowed significant hypoglycemic effect when administered intranasally in dry powder form to rats.

5) CNS delivery through nasal route

The two extracellular transport mediated routes could underlie the rapid entrance of drug into the brain which can occur within minutes of intranasal drug administration. In the first extracellular transport based route intranasally administered substances could first cross the gap between the olfactory neurons in the olfactory epithelium which are subsequently transported in to the olfactory bulb.

In the second extracellular transport based route, intranasal administered substances may be transported along trigeminal nerve to by pass BBB. After reaching the olfactory bulb of trigeminal region the substances may enter into to other regions of brain by diffusion, which may also be facilitated by perivascular pump that is driven by arterial pulsation. Delivery of drugs to the central nervous system (CNS) remains a challenge in the development of therapeutic agents for central targets due to the impenetrable nature of the drug through blood-brain barrier (BBB). The BBB obstruct the substrate penetration based on several characteristics, including lipophilicity, molecular size and specificity for a variety of ATP-dependent transport systems. Drug delivery through nasal route into CNS has been reported for Alzheimer’s disease, brain tumors, epilepsy, pain and sleep disorders.

CONCLUSION

Considering the potential benefits from nasal route of administration, we should expect to see a range of novel nasal products reaching the market in the near future. They will include not only drugs for local treatment but also for systemic protection against infections. The development of drugs for directly target the brain in order to attain a good therapeutic effect in CNS with reduced systemic side effects. Nasal drug delivery can be affected by several factors e.g. Biological Factors, Physiological factors, Physicochemical Properties of Drugs, Physicochemical Properties of Formulation. Nasal spray drug products contain active ingredients dissolved or suspended in solutions or mixtures of excipients in nonpressurized dispensers that deliver a spray containing a metered dose of the active ingredient. Critical characterization test for nasal spray includes spray pattern, droplet size distribution, Spray Content Uniformity these depend on formulation as well as device properties.

REFERENCES
