

#### **REVIEW ARTICLE**

#### FORMULATION CONSIDERATION ON AQUEOUS NASAL DOSAGE FORM AND ITS EVALUATION PARAMETER - A REVIEW



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**ABSTRACT** : Nasal Route is an attractive method of vaccination and nasal drug delivery that provides immediate absorption and the desired results. The Nasal route is best suited for those medications that can be taken orally for diarrhoea or hepatic first-pass metabolism. The article reviews nasal body composition and hydraulic spray formulation as pre-formulation studies that include PKa, water solubility, bright light, lipophilicity. These pH adjuster or buffer systems are selected as excipient, processing and distribution of invitro analytical test particles, Spray pattern, plume geometry, distribution of aerodynamic particle size.

Keywords: Nasaldrug delivery, Nasal body composition, Nasal Spray, in-vitro characterization.

#### 1. Introduction:

The respiratory tract is divided into regions: the nasopharyngeal airway (upper respiratory tract) and tracheobronchial and pulmonary airways (lower respiratory tract). One-third of the inner nasal cavity viewed at the cross section reveals the central septum separating the two pores. This region, including the closest portion of the lower and middle turbinates, is not included (Fig. 1). Flesh's are spaces made up of two turbinate doors on the lower and middle<sup>(1)</sup>. After one-third of the nasal cavity, removal of the embedded particles occurs with a slight spread of the mucous membrane in the ciliated areas near the lower and middle tissues, followed by rapid removal of mucociliary from the nasopharynx where it is swallowed. The nose serves both as an airway and also as an air conditioner for filtering air, heating and air conditioning. Larger particles trapped in the nasal filter pass more quickly (e.g., minutes compared to the hours or weeks of the bronchi and alveoli, respectively). In the anterior region of the nose (approximately 1.5 cm from the nares), the airways are blocked on each side in an area of only 30 to 40 mm2 where the nasal valve is located. when you get into turbinate's<sup>(2)</sup>.In vitro studies using human nose fungus

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and in vivo studies in people using gamma scintigraphy under natural respiratory conditions have shown that particles delivered by intranasal spraying devices are inserted into the inner regions of the nasal cavity especially between the nasal valve and ciliated epithelium (anterior turbinate. Particles affect a layer of mucous membranes that cover the surface, beneath which is a layer of epithelial cells identified directly in the pharynx. The site of implantation and the degree of clearance are very important for local anesthetic drugs that work locally. Particles> 5-10 mm in diameter (typically intranasal intramuscular spraying) do not penetrate the airways of the lungs, but are usually deposited in areas entering the respiratory tract. Particles <5 mm are thus considered to be respiratory and are inserted into the lungs. The particles <1 mm are deeply inhaled by the airways of the lungs, but receive less gravitational force and may be released without inhalation during normal breathing. The region below this (effectively the visible "inner" area of the outer nasal cavity) indicates improper  $absorption^{(3)}$ .

Nasal spray products contain active therapeutic ingredients (drug additives) dissolved or suspended in solutions or mixtures of substances (e.g., antiseptics, viscosity modifiers, emulsifiers, and buffering agents) in non-compressed distributors using spray pumps. (FDA,1999.)There are a variety of factors that contribute to the development of liquid nasal products that need to be considered during production and that must meet the needs of the clinical and medical markets<sup>(4).</sup>

Technical challenges that need to be considered when performing nasal water formations :

- Drug administration in one or two noses.
- Drug melting contributes to the formation of a form of congested water i.e. it acts as a solution or in the form of a suspension. In the form of a solution, if the volume is adjusted it would require a permeation enhancement or whether the additives in the formulation would melt. Another form of drug degradation leads to the formation of a suspension form.
- Possible disability.

### 2. **Preformulation studies**<sup>(5)</sup>:

Physicochemical structures that need to be considered are:

- 1. PKa
- 2. Water melting.
- 3. Water stability.
- 4. Light intensity.
- 5. Lipophilicity.

The formation of congested water in the form of suspension is done if the solution form is unable to deliver the required volume. The physico-chemical suspension factors that need to be considered are:

- 1. Crystal Growth.
- 2. Physical stability.
- 3. Resettlement.
- 4. Homosexuality
- 5. Dose similarities.
- 6. Moisture and / or solvent content.

# 3. Selection Of excipients (6):

### a. pH adjusters or buffer systems:

- 1. Bathing System: Phosphate buffer systems are incorporated into the composition of a liquid fluid depending on the selected pH and ionization of the drug.
- 2. Self-efficacy system: When the drug pKa itself gives a pH 4.0 of up to 7.4 major in nasal formation, it becomes a boasting system. Therefore, during production, selecting a pH equal to pKa will make it easier to transfer to the specified pH in the buffer volume (pKa) region.

### b. Tonicity:

1. Aqueous nasal preparations are usually isotonic to ensure physiological acceptability.

### Table 1: pH adjusters

pH adjusters	<ul> <li>Acetic acid</li> <li>Citric acid</li> <li>Citric acid monohydrate</li> <li>Hydrochloric acid</li> <li>Sodium citrate</li> <li>Sodium hydroxide</li> </ul>
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#### Table 2: pH buffers

pH buffers	<ul> <li>Anhydrous Trisodium Citrate.</li> <li>Potassium Phosphate monobasic</li> <li>Sodium Phosphate dibasic</li> <li>Trisodium Citrate dihydrate</li> </ul>
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2. A choice needs to be made between ionic tonicity (e.g., saline) or nonionic (e.g., dextrose). Examples: Potassium chloride, Sodium chloride.

### c. Preservatives:

International acceptability of preservative is essential before selection of a preservative. A preservative challenge testing is required [e.g., in accordance with U.S. Pharmacopeia (USP) chapter <51> Antimicrobial Effectiveness Testing]. The test requires to covering five organisms and is usually performed over four weeks using 50 mL of formulation which is required to be done at zero-, 1-, 2- and 3-year time point of the stability program.

### Limitations of Preservatives<sup>(7)</sup>:

- Adverse effects on the nasal mucosa especially in children.
- Causes discomfort, irritation, and other side effects after long-term use.
- In case of nasal infections, preservatives affect the cilia in the nasal cavity by altering the elimination of the nasal mucus.
- Also slow down or even stopping mucociliary clearance which is the essential natural mechanism for protecting the upper airways.

### d. Flavors or sweetening agents:

A small proportion of formulation may be swallowed following the nasal delivery, thus, to mask the taste of the formulation sometimes flavors or sweetening agents added. Perceptions of taste do vary with age; therefore, pediatric formulations may have to be slightly different from adult formulations. E.g. Menthol, Saccharin sodium, Sorbitol [<10% (2.5%)].

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Table 3: Preservatives and the concentration ran
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Preservatives	Concentration range (% w/w)	
Benzoic acid (sodium benzoate)	0.1–0.2	
Benzalkonium chloride	Up to 0.1	
Thiomersal	0.003–0.01	
Chlorobutanol	0.5	
Chlorbutol	0.25	
Potassium sorbate	0.1–0.2	
Methyl paraben	0.1–0.25	

### Table 4 : Viscosity adjusters

Viscosity adjusters	Hypromellose 2910
	Hypromellose
	Pectin
	Carboxymethylcellulose sodium

### Table 5 : Surfactants

	•	Benzalkonium chloride
	•	Polyethylene glycol 3350
Surfactants	•	Polyoxyl 400 stearate
	•	Polysorbate 20
	•	Polysorbate 80

Table 6 : Co-Solvents

# e. Viscosity adjusters and surfactants:

Surfactant and viscosity adjusters are usually required for suspension systems.

f. Solvents

The solvent system used as a vehicle in aqueous nasal sprays.

# 1. PROCESSINGISSUES <sup>(8)</sup>:

It is essential to look forward to the manufacturing and processing issues that will be encountered during development of a nasal product.

For solution products:

- The rate of dissolution and mixing time required.
- Generation of membrane compatibility data.

• Polyvinylidene fluoride (PVDF), Polysulfone, or Polycarbonate is chosen as the membrane system.

For suspension products:

- Density.
- Particle size distribution.
- Particle morphology.
- Solvates and hydrates.
- Polymorphs.
- Amorphous forms.

# 2. STABILITY AND COMPATIBILITY:

The delivery device and the formulation need to be considered in the stability testing program. There should be compatibility between the active gents of the formulations with the excipients and the formulation with the delivery device.

#### ANALYTICAL ACTIVITIES AND DRUG PRODUCTION STUDIES NASAL AND NASAL AEROSOLS DESIGNS:

Analytical tests used to distinguish extracted size, spray shape, and critical structural elements such as viscosity and similarity of content.

### **IN-VITRO TESTING**<sup>(9)</sup>:

### 1. Spray pattern:

The spray pattern is used to describe the shape of the extracted spray. This is done using a non-abrasive tool made with a laser sheet. It is characterized by Dmax, Dmin, ovality rate, and location.Dmax is the approximate maximum length. Dmin is the shortest range possible. Ovality rating is Dmax rating to Dmin. Percentage is a measure of the local area of the spray pattern throughout the image area.

### 2. Plume geometry:

Plume geometry to ensure the process of molding of pump components. It is characterized by the length of the plume, the spray angle, and the width of the plume.

The spray angle is the angle of the exhaust pipe measured from the vertex of the spray cone and the spray nozzle. Plum width is the plume width at a given distance from the spray pipe. Plume height the height of the extracted plume measured from the metal end.

# 3. Droplet size distribution:

Drop size distribution is based on the principle of laser diffraction to determine the distribution of droplet size from nasal sprays. It is characterized by the distribution of volume (Dv10, Dv50, and Dv90), span, and percentage (%) less than 10  $\mu$ m. The average volume range is Dv50 which shows that 50% of the distribution is contained in smaller droplets and the other half contains larger droplets. Dv10 and Dv90 values indicate that 10% and 90%, respectively, of

distribution are contained in smaller droplets than these values. The distribution of droplet size distribution is measured by equation (Dv90 - Dv10 / Dv50).

### 4. Single actuation content:

Single actuation content used for in vitro bioequivalence. Pump delivery (PD) by container health inspection is used to indicate the delivery of drugs extracted from the nasal spray actuator against a label claim for the life of the vessel. Tests are used to verify the number of correction shots and corrections under different storage and directing conditions. Spray from the nasal cavity is collected in a collection tube or glass bottle and the weight of the drug is measured by HPLC. Pump delivery is calculated by varying the weight of the collecting tube or glass bottle before and after the firing collection. Single actuation content / SCU and pump delivery are performed at the beginning and end of the life of a multi-dose drug product unit.

### 5. Distribute the particle size of the drug:

Distribution of drug particle size is used for suspension products. In this case, following the distribution of drug particles and agglomerate size is evident.

The sample from the spray unit is sprayed on a microscope slide or filtered paper. A separate light microscope is used to analyse the size of the main drug particles presents in the sample. A histogram of particle size based on computation and a graph of the particle size of the particles is then reported. Optical microscopy combined with Raman spectroscopy imaging techniques can provide an advanced method of establishing the distribution of equal particle size between Test and Reference products.

# 6. Aerodynamic particle size distribution(10):

Cascade Impactor is used to determine the value of a drug in small particles or droplets. The value of the drug with small particles is usually measured by the Andersen Cascade Impactor (ACI) which is operated by drawing a saturated air sample with ACI at 28.3 L / min.In each phase, a stream of aerosol passes through the jets and impacts on the surface. Particles in aerosol distribution with significant inertia will remain on the intervention plate. The tiny particles pass like aerosols to the next stage of the jet.By designing the following successive sections with higher aerosol jet velocities, smaller particle sizes are collected in each subsequent phase that provide a cascade touch of separation. The ACI is assembled in a 2 L glass inlet port and pre-separator. Aerosol collected in the import port, pre-separator, and impactor are analysed using HPLC to measure drug weight. Quantity and% of drugs less than 9  $\mu$ m and weight balance are reported.

#### **CONCLUSION:**

There is a growing need for the construction and development of nasal products on the market. Therefore, there is a need to study the composition and testing parameters of nasal products. Functional compatibility with the design of the nose and device is an important aspect of the study. Similarly, the study of various interconnected objects in relation to their concentration and their effect on the nasal side and thus improved effective nasal formation considering all parameters of processing has become more important unlike other types of dosage. As the performance and function of the nose spray depends on the type of device to be properly studied. The definition of nasal spray is performed by in vitro studies such as spray pattern, plume geometry, single actuation content, distribution of drug particle size, distribution of possible particle size from parameters to test other dosage forms.

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