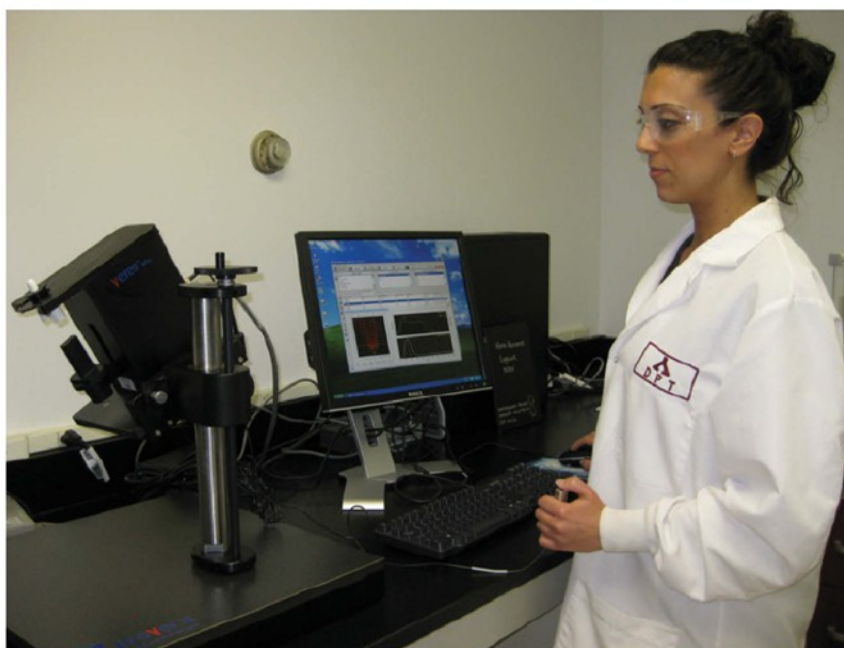


Formulation and characterization of nasal sprays

An examination of nasal spray formulation parameters and excipients and their influence on key *in vitro* tests.

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Introduction

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 nasal 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. A published report indicates that the combined sale for inhalation and intranasal drug delivery products exceeded US \$20 billion in 2009¹ and it is expected to grow.

The total surface area of the nasal cavity of an average adult is approximately 180 cm². It is richly vascularized for rapid blood flow and has microvilli in epithelial cells.^{2,3} Therefore, the nasal mucosal membrane has potential advantages for quick bioavailability and fast onset of drug action. Traditionally, nasal drug delivery was limited to treating the common cold and nasal allergies. Recently however, there has been growing interest in developing nasal drug delivery systems for systemic delivery as an alternative to oral or injectable dosage forms, including small molecular weight drugs, peptides, proteins and vaccines.^{3,4} In addition, there have been several studies since the 1970s that have suggested

intranasal drug delivery could be used to deliver drugs into the central nervous system via the olfactory epithelium, bypassing the blood brain barrier.⁵ 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.⁵⁻⁷ This article examines nasal spray formulation parameters and excipients and their influence on key *in vitro* tests.

Critical parameters affecting nasal spray formulation performance and bioavailability

Physical properties of formulations. Nasal spray formulations are broadly categorized into two types: solutions and suspensions and each can be either aqueous or non-aqueous. When formulating aqueous nasal spray products, it is critical to control properties such as pH, buffer capacity, osmolality and viscosity. The US FDA Chemistry, Manufacturing and Controls (CMC) guidance on nasal sprays recommends measurement of pH, osmolality and viscosity as part of the drug product specification.¹⁵

pH and buffer. Local pH inside the nasal cavity may have a direct effect on the rate and extent of absorption

of ionizable drugs. A study by Washington, et al.⁸ showed that, for a pool of 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. Their study showed that Sorensen's phosphate buffer at 0.13M (pH 5.8) increased the pH of the posterior part of the nose. The mildly acidic solutions produced an increase in pH, presumably due to reflux bicarbonate secretion. However, the phosphate buffer at 0.06M (pH 5.8) did not alter the pH of the posterior region of the nose, suggesting that the phosphate buffer of higher concentration may alter the pH of the posterior region of the nose. Therefore, the study by Washington, et al. emphasizes the significance of controlling pH and buffer concentration of nasal spray formulations. The pH values for several commercially-available nasal spray products are listed in Table 1. The pH of these products vary from approximately 3.5 to 7 while an optimal range for pH of the nasal spray formulation is suggested to be 4.5 to 6.5.⁹

Osmolality. 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.¹⁰ Other studies have shown that hypotonic nasal spray formulations improved drug permeability through the nasal mucosa.¹¹ Some existing marketed products have reported osmolality in the range of 300-700 mOsmol/Kg (see Table 1). The FDA suggests reporting and controlling osmolality of nasal spray formulations that contain tonicity agents.¹²

Viscosity. The FDA CMC guidance¹² recommends measuring viscosity at release and on stability for nasal spray formulations comprised of viscosity contributing agents, and where ingredients are used to control the viscosity of

Table 1

pH and osmolality of select nasal spray products on the market. Data compiled from: #Product literature, ¶The National Library of Medicine (dailymed.nlm.nih.gov) and *www.drugs.com.

Existing market products	pH	Osmolality(mOsmol/Kg) or Osmolarity (mOsmol/L)
Flonase (Fluticasone propionate nasal spray)#	5-7	Not available
Imitrex (Sumatriptan nasal spray)#	5.5	372 or 742 mOsmol/Kg for 5 or 20 mg dose respectively
Zornig (Zolmitriptan nasal spray)¶	5	420-470 mOsmol/L
Butorphanol nasal spray*	5	Not available
Desmopressin nasal spray*	3.5-6	Not available

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the product. Eccleston, et al.¹³ has reported rheological investigation of four marketed nasal sprays: Beconase (GlaxoSmithKline), Nasacort (Sanofi-Aventis), Flixonase (GlaxoSmithKline) and Nasonex (Merck). The products they investigated exhibited shear thinning, thixotropic behavior. Their study suggested that high viscosity, rather than thixotropy, was the controlling factor for prolonged residence time of the spray in the nasal cavity.

Excipient selection. As mentioned previously, both pH and tonicity of the formula may have a significant influence on performance. In addition to buffer salts, several types of excipients are required for a stable nasal spray formulation. These include solvents and co-solvents to keep the active pharmaceutical ingredient (API) in the dissolved state, as well as preservatives for non-sterile products. If the formulation is a suspension or emulsion, surfactants and/or emulsifying agents, stabilizers

and suitable oil-phase components are required. If vehicles such as liposomes or nanoparticles are used to encapsulate the API, then lipids and vehicle components also form part of the excipients. Although there are a host of surfactants, emulsifying agents, solvents, co-solvents and oils available, only a limited number of excipients are listed in the US Food and Drug Administration (FDA) Inactive Ingredients Guide (IIG) for nasal spray products. Table 2 lists some key excipients and their IIG dosage limits, as reported in the FDA IIG database for nasal spray formulations.

Improving residence time in the nasal cavity. By increasing the residence time of the medication on the nasal mucosal membrane, the chance of drug absorption through the nasal mucosa is improved.⁹ (This is challenging, however, because as part of normal nasal function, foreign particles are removed naturally as quickly

Table 2

Select excipients used in nasal spray formulations; their FDA IIG (Inactive Ingredient Guidance) limits for nasal route, spray or aerosol dosages; and their functions. (Compiled from <http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>)

Ingredients	IIG limit for nasal route and spray or aerosol dosage, % w/w	Function
Alcohol, 200 proof	2	Co-solvent
Anhydrous dextrose	0.5	Tonicity adjusting agent
Anhydrous trisodiumcitrate	0.0006	Buffering agent
Benzyl alcohol	0.0366	Preservative
Benzalkonium chloride	0.119	Preservative
Butylated hydroxyanisole	0.0002	Antioxidant
Butylated hydroxytoluene	0.01	Antioxidant
Cellulose microcrystalline/ Carboxymethyl cellulose sodium	2	Suspending agent, Stabilizer
Chlorobutanol	0.5	Preservative
CMC-Na	0.15	Suspending agent
Edetate disodium	0.5	Chelator, Antioxidant synergist
Glycerin	0.233	Humectant
Hydrochloric acid	Not reported	pH adjusting agent
Methylparaben	0.7	Preservative
Oleic acid	0.132	Penetration enhancer
PEG 400	20	Surfactant, Co-solvent
PEG 3500	1.5	Surfactant
Phenylethyl alcohol	0.254	Preservative and/or Masking agent
Polyoxyl 400 stearate	15	Surfactant
Polysorbate 20	2.5	Surfactant
Polysorbate 80	10	Surfactant
Propylene glycol	20	Co-solvent
Propylparaben	0.3	Preservative
Sodium chloride	1.9	Tonicity agent
Sodium hydroxide	0.004	pH adjusting agent
Sulfuric acid	0.4	pH adjusting agent

as possible.) A common approach is increasing the viscosity of the formulation by incorporating viscosity-enhancing agents, which can also act as muco-adhesives. However, it has been reported that high viscosity impacts droplet size distribution, resulting in altered deposition in the nasal cavity.¹⁴ Kulkarni, et al.¹⁵ have reported that formulations with hydroxyethylcellulose (HEC) as a muco-adhesive and gelling agent formed large droplets and, above a certain concentration of HEC, the plume was distorted.

Use of penetration enhancers. Chemical compounds that increase the penetration of drugs through the skin are known as penetration enhancers. Commonly-recognized categories of penetration enhancers are solvents, co-solvents, ionic and some non-ionic surfactants, and some fatty acids, including oleic acid. Some common penetration enhancers for mucosal membranes, including polymeric materials, are reported.¹⁶ Certain lipids are known to be penetration enhancers for topical formulations. A study of a nasal spray comprised of desmopressin encapsulated in liposomes has been reported.¹⁷ The results showed an increased permeation of drug from the liposomal formulation compared to the solution of the drug alone, suggesting that liposomes helped the drug to penetrate the mucosal membrane.

Non-aqueous nasal sprays. Prescription nasal spray products on the market are mostly aqueous formulations. Although patents covering non-aqueous nasal sprays formulations containing poorly water soluble drug substances are reported,^{18,19} excipients such as propylene glycol and PEG 400 are reported to cause local irritation and hyperosmolarity.²⁰ Also, acute damage to nasal mucosa by isopropyl alcohol is reported in animal models and similar effects are suspected in humans.²¹ Therefore, non-aqueous nasal spray formulations are suspected to have increased levels of safety risk, particularly in the case of chronic use. The FDA has recently accepted a new drug application (NDA) for a non-aqueous (dry) beclomethasone dipropionate nasal spray for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) which is formulated with a hydrofluoroalkane propellant.²²

Characterization of nasal sprays

Commonly, the FDA CMC guidance¹² on nasal sprays is followed when generating product development documentation. The guidance document recommends several analytical tests, including mean delivered dose (shot weight), dose content uniformity and characterization of the spray plumes for spray pattern, plume geometry and droplet size distribution. These tests are aimed at ensuring the "sameness" of the dose throughout the life of the product and from batch to batch. For determination of dose weight, dose content uniformity and plume characteristics, the FDA recommends use of an auto-

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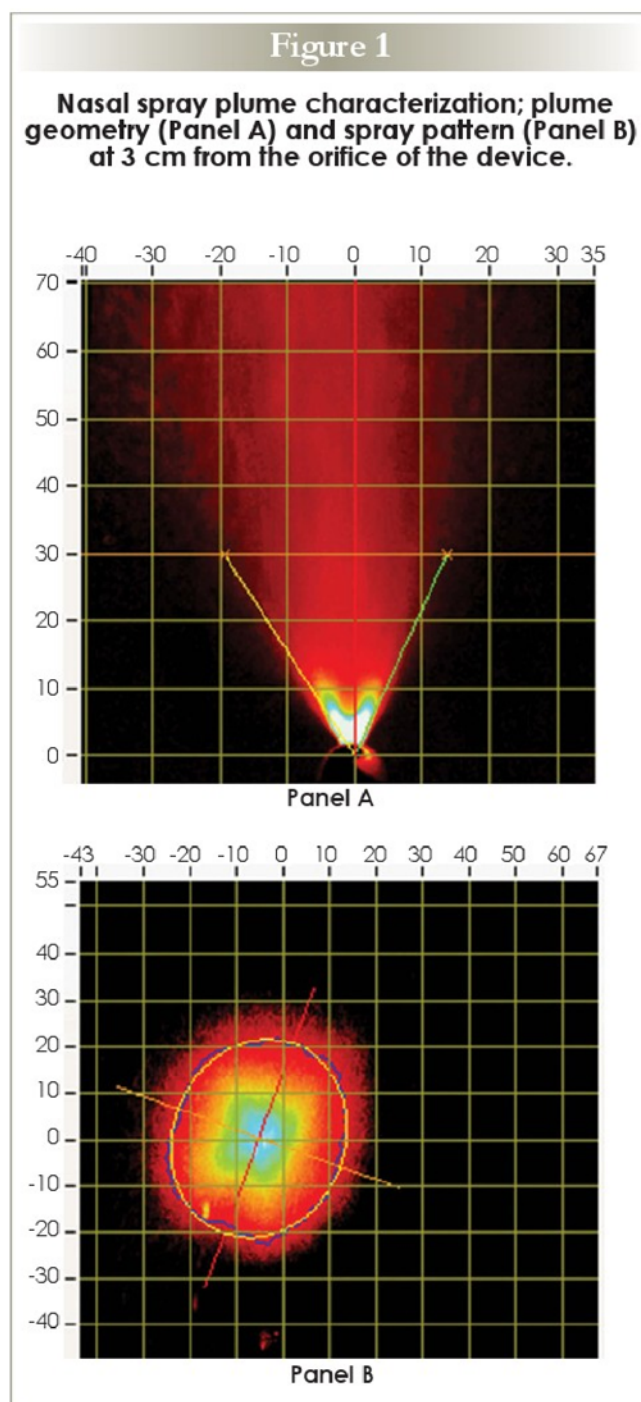
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mated actuator to eliminate the variability arising from repeated hand actuations. The actuation parameters include stroke length (displacement in mm the spray device is squeezed), velocity (or force) and acceleration of squeezing. The actuation parameters are likely to vary among brands of devices and dose volumes (which may range from 25-100 μl per spray) and within patient populations (e.g. young, adult or senior). Therefore, developing correct actuation parameters for a selected device and for the target patient population is important. Once developed, the same set of actuation parameters is used for characterization of the nasal spray for dose weight, dose content uniformity and plume characterization.

Spray pattern measures the ovality (ratio of maximum to minimum cross section diameter of the plume) of the spray at desired distances from the tip of the spray bottle (typically at 3 cm and 6 cm from the tip). Plume geometry measures the plume angle at the origin of the plume and is determined for plume lengths of 3 cm and 6 cm from the origin, at two side views (90° to each other relative to the axis of the plume). Examples of characterization of a nasal spray plume for plume geometry (plume angle) and a spray pattern (cross section of the plume) are shown in Figure 1. Droplet size distribution is a critical parameter and its control is crucial for nasal spray products.¹² Droplet size distribution depends on both the formulation and the device. For nasal sprays, the use of laser diffraction has become the industry standard for determining droplet size distribution. Measurement provides size distribution at $D(v,0.1)$, $D(v,0.5)$, and $D(v,0.9)$ thresholds (corresponding to undersize at 10%, 50% and 90% by volume distribution, respectively). The FDA suggests reporting of the size distribution data at $D(v,0.1)$, $D(v,0.5)$, and $D(v,0.9)$ thresholds, along with the percent of droplets (by volume) under $10 \mu\text{m}$ and span $[(D(v,0.9) - D(v,0.1)) / D(v,0.5)]$. Droplet size distribution studies are also performed at 3 cm and 6 cm from the nozzle of the spray bottle, to be consistent with spray pattern and plume geometry measurements. Larger droplets will tend to drip out of the nose. Conversely, droplets smaller than $10 \mu\text{m}$ may travel deeper into the nasal cavity and reach the lungs, which is not the intended delivery site. Therefore, it is critical to maintain the population of droplets less than $10 \mu\text{m}$ at a minimum level. Analysis of aerodynamic particle/droplet size by cascade impaction is also recommended for nasal inhalation products.¹² However, during the development of new nasal drug spray formulations, cascade impaction may be necessary in Bioavailability and Bioequivalence (BA-BE) studies to demonstrate safety of the formulation by 1) quantifying the mass of drug in small droplet (BA studies) and 2) showing that the mass of the drug in small droplets of the test product, is less than or equivalent to that of the reference product (BE studies).²³



For nasal sprays, a uniform circular plume with an ovality ratio close to 1, $D(v,0.5)$ of $30\text{-}70 \mu\text{m}$, and $D(v,0.9) < 200 \mu\text{m}$ with a narrow span could be considered an ideal plume. It is known that excipients, and their level in nasal spray formulations, influence the physical properties of the formulation, including viscosity and surface tension. These, in turn, can critically influence the spray pattern and droplet size distribution of the product. In a previous study, Kulkarni, et al.¹⁵ have shown that the spray pattern of a nasal formulation was not circular in the presence of polysorbate 80 at 0.1 and 0.5% (w/w), whereas a non-polymeric surfactant showed a uniform circular spray pattern with an ovality ratio close to 1. When 2% hydroxyethylcellulose was used in the formula, the median droplet

size, $D(v_{0.5})$, was 173 μm , and $D(v_{0.9})$ was $>300 \mu\text{m}$, which is not desirable because such a formulation may tend to drip out of the nose.

Conclusion

Plumes of nasal sprays are influenced by the presence of excipients and their levels in the formulation. A nasal spray formulation that shows a uniform plume, spray droplets that do not drip down the nose and a minimal percentage of droplets less than 10 μm in diameter is considered a desirable formulation. Therefore, when formulating nasal spray products, it is critical to choose the appropriate excipients and maintain their optimum levels in the formulation.

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