DPT Thought Leadership
Issue 3

ENSURING A STREAMLINED APPROACH FOR NASAL SPRAY PRODUCT DEVELOPMENT & MANUFACTURING

INTRODUCTION

Nasal sprays are comprised of one or more therapeutically active ingredients that are either dissolved or suspended in solutions in non-pressurized dispensers. The most common use is for allergy-related symptoms, such as allergic rhinitis. Nasal sprays can be unit dose, bi-dose or multi-dose devices. The 2002 U.S. Food and Drug Administration guidance on "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation" describes several tests for characterizing nasal spray drug products. The regulatory guidance may have some differences in, or additions to, testing requirements in Europe, Canada or other countries compared to that in the United States.

Because the efficacy of the drug product depends on the ability of the spray device to deliver reproducible plumes and uniform dose content, some aspects of nasal spray development are unique such as formulation, container closure system, plume characterization, manufacturing and stability testing. Therefore, these aspects need to be carefully considered during the development program.

This white paper aims to provide a comprehensive overview of the CMC guidance by the U.S. Food and Drug Administration and present a streamlined approach for development and manufacture of nasal spray products.

RATIONALE/NEED

The development of a successful nasal spray drug product is an intricate process that requires a good understanding of interactions between the formulation and the delivery device.

As the delivery device plays such a crucial role in the success of nasal sprays, it is beneficial to rely on a contract development and manufacturing organization (CDMO) that can provide expert advice on nasal spray drugs as well as the type of packaging that should be used. The CDMO should also be able to identify potential problems and advantages of various packaging options.

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SOLUTION

In the pre-formulation and formulation stages of development, the physical characterization of nasal aerosol drug products must include a thorough examination of:

- Solubility and particle characteristics
- API / excipient compatibility
- Plume characterization: Spray pattern, plume geometry and spray droplet size
- Spray content uniformity
- Container closure testing, under the standards found in USP <671>

Challenges include:

- Balancing droplet particle size so it stays in the nasal cavity. Droplets must not be so small that they go into the lungs, and not so large that they drip out quickly.
- The use of muco-adhesives can help the drug adhere within the nasal cavity and reduce the effects associated with nasal clearance.
- Formulas with large molecules, such as proteins and peptides. Larger molecules provide challenges relating to cellular penetration before getting into the bloodstream. Penetration enhancers can be used to reduce this effect.
- Spray characterization, an area in which clients often seek advice and help. A plume that coats the largest possible area of the nasal cavity, for absorption into the blood stream, is ideal, and the CDMO should be able to determine the best delivery device to achieve that goal with a given formulation.

Excipients

Typical excipients used in nasal sprays include: water, preservatives, buffer salts, viscosity modifying agents, suspending agents, pH adjusting agents and flavors. As the excipients may significantly influence the spray characteristics[1], an investigation of the effect of these materials within the formulation, as well as their compatibility with the active drug, are critical aspects of the product development.

The following page contains a list of some typical excipients used in nasal spray aerosol products along with their functions and typical concentrations used in the formulation[2]:

Excipients Used in Aqueous Nasal Products		
Excipient	**Function**	**Typical Conc.**
Acetic and citric acids	pH adjustment/ buffer	0.12%/ 0.10%
Sodium hydroxide/ hydrochloric acid	pH adjustment	No range
Sodium acetate, citrate, and phosphates (mixed), potassium phosphate (mixed)	Buffer	No range
Edetate disodium	Metal chelator/preservative enhancer	0.01%
Benzalkonium chloride	Preservative (known effect on cilia)	0.01-0.02% w/v
Benzethonium chloride	Preservative	No range
Benzyl alcohol	Preservative	Not listed by FDA
Chlorobutanol	Preservative (known effect on cilia)	0.05-0.1%
Methylparaben	Preservative (known effect on cilia)	0.033%
Phenylethyl alcohol	Preservative	0.25%
Phenylmercuric acetate	Preservative (known effect on cilia)	Not listed by FDA
Propylene paraben	Preservative (known effect on cilia)	0.017%
Thimerosal	Preservative (no effect on cilia at 0.01%)	Not listed by FDA
Potassium chloride	Tonicity adjustment	Not listed by FDA
Sodium chloride	Tonicity adjustment	0.5-0.9%
Me-OH- Pr cellulose	Viscosity adjustment	<1%
Na CMC	Viscosity adjustment	<1%
Microcrystalline cellulose	Viscosity adjustment	<1%
Ethanol	Solvent	No range
Glycerol	Solvent/ tonicity adjustment	1.0-2.5%
Glycine	Solvent/ tonicity adjustment	No range
PEG (mixed)	Solvent	<5%
PG	Solvent	<10%
Glyceryl dioleate	Solvent	<10%
Glyceryl monoleate	Surfactant	<7%
Lecithin	Surfactant	<5%
Polysorbate 20 & 80	Surfactant	<2%
Triglycerides	Cosolvent	<2%
Menthol	Flavoring agent	No range
Saccharin sodium	Flavoring agent (sweetener)	No range
Sorbitol	Flavoring agent (sweetener)	<10% (2.5%)

Extractables and Leachables

An important part of the stability testing of a drug product is an examination of extractables and leachables in a packaging component. An extractable is any chemical species that can be extracted from a packaging component under "harsh" conditions in laboratory studies. A leachable is an extractable that actually migrates (partitions) into a drug product under storage conditions.

Extractable data typically is supplied by the device supplier. Leachables are tested as part of stability protocol. Testing methods include liquid chromatography-mass spectrometry and gas chromatography-mass spectrometry.

A typical approach includes these steps:

1. Review supplier's (supplier of device and pumps) specifications for extractables
2. If necessary do additional extractable studies (identify, assess risk, and validate the method)
3. Perform leachables study[3,4] as part of stability protocol - USP <381> (for elastomers) and <661> (for plastics and other polymers)

Manufacturing

Selection of quality valves and devices appropriate for a given drug product is an important part of the manufacturing process. It is essential to review the manufacturers' specifications and to check their dimensions for the assembly line.

Quality performs physical and chemical characterization analytical methods using a scaled-up drug product batch.

Here are some of the test requirements according to the 2002 FDA Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products — CMC guidance document:

Physical, Chemical & Microbiological Tests
Description of drug product: appearance and color
Identification of drug substance in drug product
Assays: API, and drug product
Impurities and degradation products
Particulate matter
Preservatives and stabilizing excipients assays
Microbial limits, Preservative efficacy, Sterility maintenance
pH, Osmolality, Viscosity
Particle size distribution (for suspended formulations)
Net content, weight loss on stability and effect of device orientation
Leachables
Priming and re-priming in various orientations, effect of resting time
Effect of temperature cycling

Spray & Device Characterization
Pump-to-pump reproducibility
Spray content uniformity
Droplet size distribution
Spray pattern and plume geometry
Device robustness
Effect of dosing orientation
Tail-off characteristics: profiling of spray near container exhaustion
Pump delivery
Aerodynamic particle size (for inhalation sprays)

CONCLUSION

With many products, packaging often is a secondary consideration. But with nasal products, the packaging or delivery device is a more important consideration. The packaging used with nasal sprays plays a crucial role in:

- Uniformity of the size of the dose delivered with each use
- Spray droplet size — to make sure the droplets are neither so large that the product simply drips out of the nose, nor so small that they are inhaled into thelungs
- Size of plume to properly coat the inside of the nose, as it is no good to have an elegant product that goes to waste by squirting out in a solid stream A CDMO that understands the importance of matching the formulation with the proper delivery device will offer the best means of bringing to market a pharmaceutical product that performs as intended.

REFERENCES

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DPT is a contract development and manufacturing organization (CDMO) providing companies the best solutions to their sterile and non-sterile pharmaceutical development and manufacturing needs through innovation, technology, and service. Specializing in semi-solid and liquid dosage forms, DPT has a reputation for quality, unmatched technical expertise, extensive manufacturing capabilities, and an exemplary regulatory compliance record. With five cGMP facilities in San Antonio, Texas, and Lakewood, New Jersey, DPT offers full-service outsourcing solutions, including stand-alone development, site transfers, state-of-the-art manufacturing, packaging, and worldwide distribution.

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