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Review

Analytical Challenges and Regulatory Requirements for Nasal Drug Products in Europe and the U.S.

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Abstract: Nasal drug delivery can be assessed by a variety of means and regulatory agencies, e.g., the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have published a set of guidelines and regulations proposing *in vitro* test methods for the characterization of nasal drug products. This article gives a summary of the FDA and EMA requirements regarding the determination of droplet size distribution (DSD), plume geometry, spray pattern and shot weights of solution nasal sprays and discusses the analytical challenges that can occur when performing these measurements. In order to support findings from the literature, studies were performed using a standard nasal spray pump and aqueous model formulations. The aim was to identify possible method-, device- and formulation-dependent influencing factors. The literature review, as well as the results from the studies show that DSD, plume geometry and spray pattern are influenced by, e.g., the viscosity of the solution, the design of the device and the actuation parameters, particularly the stroke length, actuation velocity and actuation force. The dominant factor influencing shot weights, however, is the adjustment of the actuation parameters, especially stroke length and actuation velocity. Consequently, for routine measurements assuring, e.g., the quality of a solution nasal spray or, for *in vitro* bioequivalence studies, the critical parameters, have to be identified and considered in method development in order to obtain reproducible and reliable results.

Keywords: nasal drug delivery; regulatory aspects; test methods; nasal sprays

1. Introduction

The most prominent way of intranasal drug delivery is the administration of locally acting drugs in order to treat nasal congestion, infections and allergic rhinitis [1]. However, the nasal route can also be used for the systemic delivery of drugs for the therapy of various diseases, like osteoporosis and migraine, as well as for pain management and also for the administration of vaccines [2]. It is a painless, non-invasive delivery route, resulting in a rapid drug onset of action, due to the high vascularization of the nose and high permeability of the nasal mucosa under avoidance of first pass metabolism [3]. These advantages lead to high patient convenience and compliance.

For nasal drug delivery, there are several dosage forms available. The most popular examples are nasal sprays and nasal drops for which the drug can be formulated as a solution or suspension. Alternative dosage forms are the pressurized nasal aerosols and nasal powders. Typically, aqueous nasal spray formulations contain the drug, as well as bioadhesive polymers, surfactants, tonicity agents and, in some cases, penetration enhancers [4]. Bioadhesive polymers, like sodium carboxymethyl cellulose, are often used to increase the viscosity of the formulation in order to stabilize the suspension or to increase the residence time in the nasal cavity to modify drug absorption [4,5]. Surfactants can be included in the formulation to solubilize the drug in case of poor solubility or to increase the wettability [6].

Besides the formulation, also the delivery device plays an important role in nasal drug delivery, and only the combination of both, device and formulation, determines the properties of the final nasal drug product. This makes the development of nasal drug products more complex, since the variability of the formulation and the device have to be taken into account [5]. Therefore, the analytical requirements for the approval of nasal drug products exceed those for solid dosage forms [7]. For the *in vitro* characterization of nasal drug products in the development phase, as well as for quality control and bioavailability/bioequivalence studies, regulatory agencies, like the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have published guidelines and regulations proposing various test methods [8–11]. Tables 1 and 2 give a summary of the recommended tests for the different nasal drug products. However, in order to obtain reliable results, the test methods need to be validated, and in this context, it is essential to know the factors that can influence the measurements. In some studies, it could be shown that the spray characteristics can be influenced by the design of the device, by the formulation properties, like viscosity and surface tension, and by the handling of the device, *i.e.*, the actuation parameters [5,12–18]. Additionally, the selected technique and the set-up of the measurements can also have an effect on the results and have to be considered during method development.

Table 1. Tests recommended for the finished drug product specification by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (standard quality tests are not listed).

Test	Pressurized metered dose nasal sprays	Nasal powders	Single and multiple use nasal drops	Single and multiple use nasal sprays
Specifications for the drug product				
Pump/valve delivery	yes [#]			yes [#]
Delivered dose/content uniformity		yes	yes, for multiple use drops	yes, for multiple use sprays
Dose content uniformity through container life	yes [#]			yes [#]
Content uniformity/uniformity of dosage units	no *	no *	yes, for single use drops *	yes, for single use sprays *
Mean delivered dose	yes *	yes *	yes, for multiple use drops *	yes, for multiple use sprays *
Spray pattern	yes [#]			yes [#]
Particle/droplet size distribution	yes	yes	no	yes
Particle size distribution of API	yes, for suspensions [#]			yes, for suspensions [#]
Microscopic evaluation	yes, for suspensions [#]			
Particulate matter	yes [#]			yes [#]
Microbial limits	yes	yes	yes	yes
Preservative content	no *	no *	yes, if present *	yes, if present *
Preservatives and stabilizing excipients assay				yes [#]
Sterility	no *	no *	yes, if product is sterile *	yes, if product is sterile *
Net content/minimum fill	yes [#]			yes [#]
Number of actuations per container	yes *	yes *		yes, for multiple use sprays *
Weight loss (stability)				yes [#]
Leachables (stability)	yes [#]			yes [#]
Osmolality				yes [#]
Viscosity				yes [#]
Appearance and color of content and container closure system	yes [#]			
Water or moisture content	yes	yes	no	no
Dehydrated alcohol content	yes, if used as a cosolvent [#]			
Leak rate	yes	no	no	no

Table 1. *Cont.*

Test	Pressurized metered dose nasal sprays	Nasal powders	Single and multiple use nasal drops	Single and multiple use nasal sprays
Specifications for the drug product				
Pressure testing	yes, if cosolvent or more than one propellant is used [#]			

Explanatory note: "yes", the test is recommended for the particular drug product; "no", the particular drug product is excluded from the test; blank, no specific details in the guidelines are available; [#] FDA only requirement; * EMA only requirement; API, active pharmaceutical ingredient.

This article gives an overview of the regulatory requirements regarding the determination of droplet size distribution (DSD), plume geometry, spray pattern and shot weights. These tests, among others, are required in development and *in vitro* bioequivalence studies, as well as in quality control matters. In addition to the regulatory requirements, analytical challenges and possible influencing factors related to the device, formulation composition and selected method/technique that affect nasal spray characteristics are reviewed. In order to support findings from the literature, studies comprising the determination of DSD, plume geometry, spray pattern and shot weights were performed using model formulations and a standard nasal spray pump.

Table 2. Tests recommended for nasal drug product characterization/development studies by the FDA and the EMA.

Test	Pressurized metered dose nasal sprays	Nasal powders	Single and multiple use nasal drops	Single and multiple use nasal sprays
Drug product characterization/development studies				
Physical characterization	yes, for suspensions *	yes *	yes, for suspensions *	yes, for suspensions *
Priming and repriming (in various orientations)	yes	no	no	yes
Plume geometry	yes [#]			yes [#]
Microscopic evaluation	yes, for suspensions [#]			
Effect of resting time	yes [#]			
Shaking requirements	yes, for suspensions	no	yes, for suspensions	yes, for suspensions
Minimum fill justification	yes *	yes *	yes *	yes *
Extractables/leachables	yes *	no *	yes *	yes *
Performance after temperature cycling	yes	no	no	yes
Effect of environmental moisture	yes *	yes *	no *	no *
Cleaning instructions	yes	yes	yes, for multiple use drops	yes, for multiple use sprays

Table 2. *Cont.*

Test	Pressurized metered dose nasal sprays	Nasal powders	Single and multiple use nasal drops	Single and multiple use nasal sprays
Drug product characterization/development studies				
Device robustness	yes	yes	yes	yes
Profiling of sprays near container exhaustion (tail off characteristics)	yes #			yes #
Delivered dose uniformity through container life	yes *	yes *	yes, for multiple use drops *	yes, for multiple use sprays *
Effect of storage on PSD	yes, for suspensions #			yes, for suspensions #
Particle/droplet size distribution	yes	yes	no	yes, for multiple use sprays
Preservative effectiveness (and sterility maintenance)	no	no	yes, if present	yes, if present
Photostability	yes, if drug is exposed to light #	yes, if drug is exposed to light #	yes, if drug is exposed to light #	yes, if drug is exposed to light #
Actuator/mouthpiece deposition	yes	yes	no	yes *
Determination of appropriate storage conditions	yes #			
Stability of primary (unprotected) package	yes #			yes #
Delivery device development	yes	yes	yes	yes
Microbial challenge	yes #			
Effect of dosing orientation				yes #
In vitro dose proportionality	yes, for suspensions in multiple strengths #			yes, for suspensions in multiple strengths #
Low temperature performance	yes *	no *	no *	no *

Explanatory note: "yes", the test is recommended for the particular drug product; "no", the particular drug product is excluded from the test; blank, no specific details in the guidelines are available; # FDA only requirement; * EMA only requirement; and PSD, particle size distribution.

2. Experimental Section

2.1. Materials

Mechanical nasal spray pumps delivering 100 µL of formulation per actuation were provided by Aptar (Radolfzell, Germany). Water was used in double-distilled quality (FinnAqua 75, San Asalo-Sohlberg Corp., Helsinki, Finland). Sodium carboxymethyl cellulose (Tylopur C 30 G) was obtained from Clariant (Muttenz, Switzerland) and polysorbate 80 from Uniqema (Snaith, UK).

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