Investigating orthogonal in vitro analytical approaches to demonstrate bioequivalence of nasal suspension formulations

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Summary

The objective of this study was to investigate a range of orthogonal analytical tools to investigate API particle size in nasal suspensions formulations to demonstrate comparability between test and reference nasal suspensions. The application of these approaches are designed to be utilized to support in vitro bioequivalence of nasal suspension drug products. The aim of this proposal is to present a pathway whereby it may be possible to demonstrate Q3-equivalence between test and reference nasal suspension formulations. For such an approach to be successful, the application of advanced analytical tools to characterize formulation and raw material properties within the nasal suspension formulation are required.

Our proposed approach utilizes a combination of orthogonal techniques to support characterization nasal suspension formulations. These techniques include morphology directed Raman spectroscopy (MDRS) and UniDose-enabled dissolution testing. We will assess the API particle size in the formulation using MDRS to enable quantification of the size, shape and distribution of the formulation microstructure, which will be further investigated using UniDose-enabled dissolution testing. Together, these data will provide a systematic approach to quantify and compare the microstructure of nasal suspension formulation systems. Moreover, the structure-function of the formulation will be investigated rheological analysis.

Introduction

Nasal suspension drug products consist of API particles suspended in an aqueous system in the presence of a range of different excipients. For suspension nasal products, the API particle size is a key critical material attribute, which will affect emitted API particle size and regional deposition of API in the nose. In addition, the particle size of the API will affect the rate of dissolution and permeability at site of deposition in the nasal epithelium and thereby systemic exposure of the API from the nose[1].

The paucity of validated methods for characterizing API-specific drug particle size and particle size distribution (PSD) in nasal formulations has resulted in limited understanding of the relationship between API PSD, regional deposition in the nasal cavity, dissolution and absorption of the API from the nose[2]. Although PSD can be readily determined by a number of methods prior to formulation into a finished product, the primary challenge has been to determine the PSD of the drug substance in the finished nasal aqueous suspension products in the presence of undissolved excipients[3]. Excipients such as microcrystalline cellulose typically have a median particle size that is larger than the API. However, excipients often exhibit a broad PSD and a substantial number of excipient particles may exist in the same size range as the drug substance, thus complicating drug substance particle size determination. Raman microscopy is a promising approach for characterising particle size of API in aqueous nasal spray suspension formulations. This approach potentially allows the chemical identification of API in situ within complex nasal formulations which can directly benefit the BE requirements for ANDAs. However, in order to detect a statistically relevant number of API particles and measure their size remains a major drawback to this method. Therefore, there is a requirement of methodological processes that can enhance the robustness of the data that Raman microscopy methods provide.

The pharmacokinetic behaviour of locally acting drugs governs their presence at the therapeutic target site. After intranasal application of the aqueous glucocorticoid suspension, the drug crystals have to dissolve in the epithelial mucus fluid layer. A sustained dissolution of drug particles contributes to a prolonged nasal contact time[4,5,6]. Since dissolution of the drug substance is directly related to the particle size of the API, the measurement of dissolution of APIs in the nasal suspension formulation is an orthogonal technique to the measurement of API particle size (i.e. differences in test and reference product dissolution can confirm similarities or differences in the API particle size in the formulation). We therefore, propose that measurement of the API dissolution of nasal suspensions is a critical measurement that links to the API particle size in suspension. Moreover, measurement of the dissolution may help to validate the particle size tools for assessing PSD of the API in suspension.

The key objective of this study was to use a combination of in-situ particle sizing of the API in the nasal suspension and dissolution testing to characterize test and reference nasal suspensions. The application of these approaches was designed to be utilized to support in vitro BE investigations of nasal suspension drug products.
Experimental Methods

Four batches (Batch 1, 2, 3 and 4) of Mometasone Furoate (0.05% w/w, Sterling, Perugia, Italy) were procured and formulated into aqueous suspension nasal sprays. The formulation design was designed to be qualitatively and quantitatively the same as reference listed drug (RLD) product Nasonex® (Merck, USA). Nasonex RLD was also sourced for the investigations (Lot No. 14MAA532A, expiry: 10/2016).

Particle size distribution analysis of the as-received API batches was performed using wet-dispersion laser diffraction particle sizing (Malvern 2000, Malvern Instruments, Worcestershire, UK).

Morphology-directed Raman Spectroscopy (MDRS) was performed on Nasonex, as-received API batches and when formulated into nasal suspension formulations was characterized using a Morphologi G3-ID (Malvern Instruments, Worcestershire, UK). Upon applying morphological filters, the chemical analysis was carried out using the Kaiser Optical Systems RamanRxn1 Spectrometer integrated in the Morphologi G3-ID equipment. The Raman spectrum for each of the particles within the same scanning area was collected using 60s of exposure time with excitation at a wavelength of 785 nm over the spectral range of 100–1825 cm$^{-1}$ at a resolution of 4 cm$^{-1}$.

The emitted dose of test and reference nasal drug products was collected using a novel aerosol collection rig, described elsewhere[7]. The collected dose was then prepared into an extraction cell that was placed into a USP II dissolution bath containing PBS and 0.05% SDS.

Results and Discussion

We have investigated the particle size of commercial drug substance supply of four batches of Mometasone Furoate using conventional laser diffraction (Figure 1). These data suggested that batches 1 and 4 were the largest and batch 2 was the smallest in terms of particle size. These API batches were manufactured as aqueous nasal suspensions to be quantitatively and qualitatively the same as the marketed Nasonex® (Merck, USA) product, but formulated with different drug substance batches with different particle size. The MDRS method was then employed to determine if the as-received drug substance particle size correlated with the formulated drug substance particle size in the formulation. Comparison of the laser diffraction and MDRS data suggested that the MDRS method was able to track the drug substance particle size in the nasal suspension formulation.

<table>
<thead>
<tr>
<th>Batch Number</th>
<th>Dv(10) /µm</th>
<th>Dv(50) /µm</th>
<th>Dv(90) /µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.81 (0.05)</td>
<td>6.01 (0.15)</td>
<td>11.94 (0.25)</td>
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<tr>
<td>2</td>
<td>0.76 (0.01)</td>
<td>1.39 (0.01)</td>
<td>2.42 (0.03)</td>
</tr>
<tr>
<td>3</td>
<td>1.14 (0.01)</td>
<td>3.97 (0.02)</td>
<td>8.11 (0.1)</td>
</tr>
<tr>
<td>4</td>
<td>2.14 (0.05)</td>
<td>6.36 (0.08)</td>
<td>12.57 (0.11)</td>
</tr>
</tbody>
</table>

Figure 1. Particle size distribution of four batches of as-received mometasone furoate API measured using a Malvern 2000 laser diffraction system.
Using a novel aerosol capture system, it was possible to determine the dissolution of the formulations made with drug substance of different particle size. These data suggested a good correlation between the percentage by volume less than 5 µm and dissolution half-life of the formulated products. Hence, an orthogonal approach combining MDRS and dissolution analysis will help support generic manufacturers to develop substitutable generic products of aqueous nasal suspensions, and ensure they have control of drug product quality. As part of this proposal we will determine the dissolution of a range of nasal US RLD products and manufactured test formulations.

Figure 2. MDRS particle size distribution of four batches of mometasone furoate API formulated into aqueous nasal suspension formulations.

Figure 3. Relationship between the percentage by volume less than 5 µm of the formulated drug substance measured by MDRS and the dissolution half-life of the drug product.
Conclusion

A combination of dissolution testing and MDRS of a nasal suspension was able to discriminate between differences in API particle size in nasal suspension formulations. Together, this approach allows characterisation of PSD of the API in the formulation and thereby facilitates comparative analysis of test and reference products. The result of these investigations may help to provide an approach to determine bioequivalence of nasal suspensions formulations using in-vitro methods.

References


