**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 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 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 particle size determination. Morphology-directed Raman Spectroscopy (MDRS) is a promising approach for characterising particle size of API in aqueous nasal spray suspension formulations. Morphological filters are utilized to allow the detection of a statistically relevant number of API particles. This approach allows the chemical identification of API in situ within complex nasal formulations which can directly benefit the BE requirements for ANDAs.

Since the measurement of the API dissolution of nasal suspensions is a critical measurement that links to the API particle size in suspension[4,5,6]. We propose that this technique is used as an orthogonal technique to the measurement of API particle size. Moreover, measurement of the dissolution may help to validate the particle size tools for assessing PSD of the API in suspension.

**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 nasal sprays. The formulation design was suggested to be qualitative and quantitatively the same as reference listed drug (RLD) product Nasonex® (Merck, USA). Nasonex RLD was also sourced for the investigations.

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 using a Morphologi G3-ID (Malvern Instruments, Worcestershire, UK).

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[7].

**Results**

**Morphology-directed Raman Spectroscopy**

We have investigated the particle size of commercial drug substance supply of four batches of Mometasone Furoate using conventional laser diffraction (Figure 2). 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.

**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**