Polymorph Identification of Drug Particles in OINDPs

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INTRODUCTION

Polymorphs are chemicals of identical molecular structure with different crystal lattice formations. Screening for polymorphs is crucial for drug research and development, since the crystal form of the active pharmaceutical ingredient (API) directly correlates with its pharmacokinetic properties. Polymorphism can also affect the quality, safety and efficacy of the drug product and ability to manufacture the drug substance with desired product stability and bioavailability (BA) [1].

There is a need for polymorph identification of drug particles in Orally Inhaled and Nasal Drug Products (OINDPs) because of the Food and Drug Administration (FDA) regulations related to reporting and confirming drug polymorphic form in the finished product [2]. Section 505(j) of the Act specifies that an Abbreviated New Drug Application (ANDA) must contain, among other things, information to show that the active ingredient in the generic drug product is the "same as" that of the Reference Listed Drug. For bioequivalence (BE) determination, it is vital to demonstrate lot-to-lot quality of the generic drug products, which include drug form polymorph stability.

In-vitro dissolution tests are common methods used to provide means to detect inadvertent changes to the polymorphic form of the drug particles, which affect drug product BA/BE. However, dissolution tests lack chemical specificity in evaluating the polymorphic purity of the active ingredient in the final product from development to scale-up, batch-to-batch comparison and stability studies. Other analytical methods, widely used for polymorph analysis, such as X-Ray Diffraction [3], cannot be applied in-situ to identify polymorphic purity of drug particles in OINDP drug products.

Ingredient-specific particle sizing (ISPS) analysis, in conjunction with polymorph identification analysis of drug-only particles in OINDPs based on Raman spectroscopy and imaging, can address these challenges in evaluating drug products, from both the BA/BE and physical perspectives.

We used one of the commercially available formulations containing a drug that has a stable crystalline polymorph, such as fluticasone (Flonase®, GSK), to illustrate a nondestructive approach of polymorph identification of drug particles in suspension formulation by Raman spectroscopy and imaging. Fluticasone propionate exists in two polymorphic forms (I and II) [4], which differ in dynamic bulk density, fluidability, flow properties and therefore can directly affect the final product. Fluticasone has a very potent anti-inflamatory action and is formulated as intranasal spray and inhaled product alone or as combination drug [5].

In this abstract, Gateway Analytical will present new qualitative and semi-quantitative methods for the examination of size and polymorph drug particle identification in finished products. Specifically, its benefits for BA/BE testing will be described using the model of fluticasone-containing nasal spray suspension formulation.

METHODS FOR POLYMORPH IDENTIFICATION OF DRUG PARTICLES

Raman spectroscopy was used to create a Raman spectral library (reference spectra) of the pure form of the drug substance (Fluticasone). Nasal spray was prepared by shaking, priming and spraying in an upright position onto an inverted aluminum-coated glass microscope slides positioned approximately 15 cm above the spray nozzle. The microscope slides were then immediately turned upright and the nasal suspension droplets were allowed to dry. Particles were randomly selected on a freshly prepared sample and a Raman dispersive spectrum was collected. A reference Raman spectrum was then used to confirm the polymorph type of fluticasone particles in the Flonase® nasal suspension formulation, both by Raman spectroscopy and RCI (Figure 3). Imaging spectrometer spectrum from each detected nasal suspension formulation particle was compared to the pure fluticasone dispersive spectrum to confirm polymorphic identity of all sized particles. All studied particles were confirmed to have the same polymorphic structure as the pure fluticasone propionate by RCI and Raman spectroscopy, allowing for the evaluation of the polymorphic purity of the active ingredient in the final product and confirmation of the chemical specificity of the drug particles. Figure 1 shows that Raman spectrum band position, Raman bandwidth and shape of the formulation particles are similar to those of the pure polymorph form of Fluticasone.

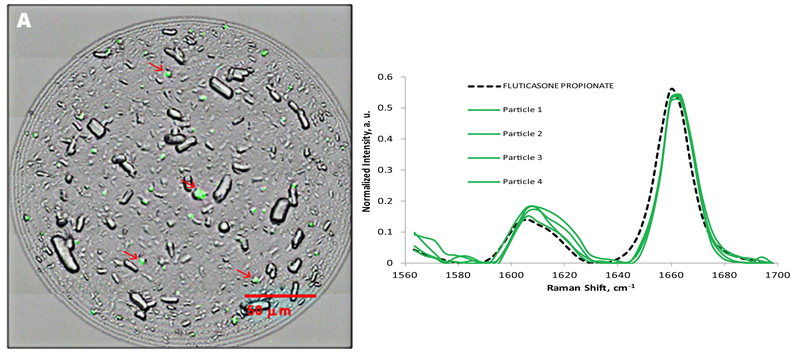

Figure 1. Representative BFR Image of randomly selected API particles (green) in Flonase® nasal spray (A), and comparison of their dispersive spectra to reference spectrum of Fluticasone Propionate pure component (B).

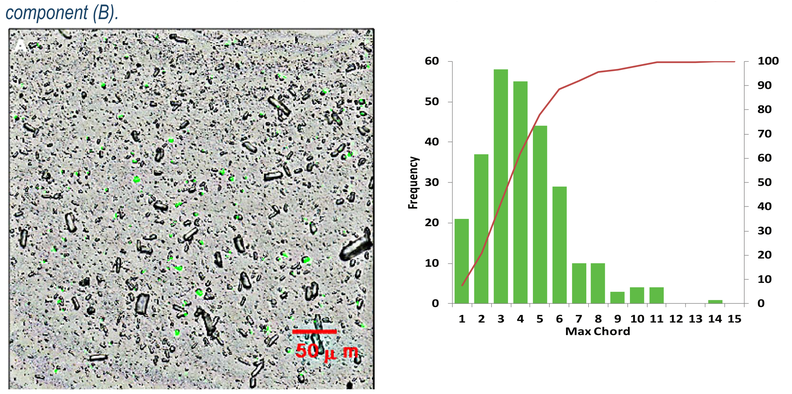

Figure 2. BFR and processed RCI fusion image (A) and particle size distribution histogram (B) of Fluticasone Propionate particles from Flonase® nasal suspension.

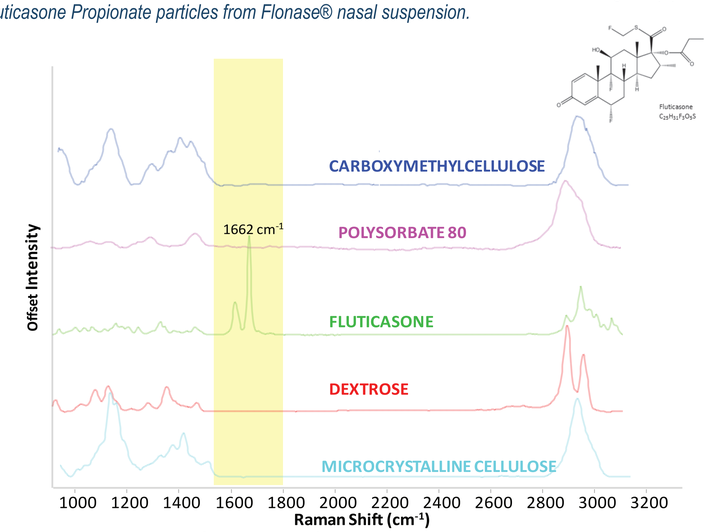

Figure 3. Raman Dispersive Spectroscopy of pure components

RESULTS AND DISCUSSION

Polymorph identification was based on comparison of the position of the Raman bands, specific for the pure form of the drug and detected from the fluticasone

Subsequently, spectral and image processing was used for ISPS [6] (Figure 2). This approach not only allows for obtaining accurate and chemically specific particle sizing, but also provides means to collect information about any drug to drug or drug to excipient agglomerates that may form in the formulation and cause an unwanted drug polymorph transition. Due to increasing interest to develop and manufacture combination drug products, especially for inhalation route of administration, evaluation of drug polymorphic forms of the engineered particles becomes especially important, since it correlates with the final dry powder efficacy [7]. RCI was already shown to be especially beneficial to study the complex microstructure/agglomeration nature of combination dry powder inhaler formulations containing fluticasone and salmeterol, as it relates to surface interfacial interactions between components of the formulation [7]. It was shown that particle size and chemical composition of agglomerated systems of both fluticasone propionate and salmeterol were different. Thus the mechanisms or engineering approaches to create chemically-specific particles of desired size and desired crystalline structure may be tested by RCI to understand dispersion of the drug particles and aerosolization performance [7]. Since the FDA recommends evaluation of the DPIs for the presence of large particles, aggregates and foreign contaminants, changes in morphology and crystal growth for both drug substance and carrier particles, it is important to use chemically-specific analytical methods, such as RCI for "release and stability purposes" [8]. Furthermore, this technique can also be used to investigate less stable forms of polymorphs (i.e. hydrate forms, such as mometasone) [9] and to assess BA/BE of OINDPs.

CONCLUSIONS

Polymorph identification by RCI and Raman spectroscopy has been shown to be a direct, nondestructive method to evaluate drug particles polymorphic purity in a suspension formulation. This reliable and reproducible method that employs automated data collection and analysis for fast and accurate simultaneous size measurements and chemical identification of each component could be used for bioequivalence testing of ANDAs.

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