Challenging the Bioequivalence Hurdles for OINDPs: Achieving Q3 Structural Equivalence

Robert Price, Gonçalo Farias, William Ganley, and Jagdeep Shur

Department of Pharmacy and Pharmacology, University of Bath, Bath, UK

KEYWORDS: Q3 equivalence, microstructure, dissolution, morphology directed Raman spectroscopy (MDRS), pharmaceutical equivalence, *in vitro* bioequivalence

SUMMARY

The 2003 Federal Drug and Cosmetic Act, Section 505(j)(8)(C), states that a drug that is not intended to be absorbed systemically can be assessed for bioequivalence (BE) by alternative *scientifically valid measurements* that can establish and detect a significant difference between the generic and the reference listed drug (RLD) in terms of safety and therapeutic effect. While pharmacokinetic (PK) studies in combination with *in vitro* based measurements have provided useful insight relating to the systemic exposure of inhaled compounds, these analyses do not provide the evidence to support therapeutic equivalence at the local site of action. In the abbreviated new drug application (ANDA) pathway for orally inhaled and nasal drug products (OINDPs), the US Food and Drug Administration (FDA) has introduced the concept of microstructural equivalence (Q3) for local acting products that are qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug products in terms of their active and inactive pharmaceutical materials. The microstructural differences in the arrangement of matter and state of aggregation within formulated and aerosolized forms of OINDPs will be dependent on the physicochemical properties of active and inactive materials, device characteristics, and processing history. Differences in Q3 at both a microscopic and macroscopic scale can manifest itself as a difference in properties that could be characterized using a combination of orthogonal *in vitro*- or *ex vivo*-based techniques. Some of the techniques currently under assessment for characterising Q3 of OINDPs include the use of morphologically directed and surface mapping Raman spectroscopy and an integrated

measurement of structure using *in vitro* dissolution and permeability kinetics. For OINDPs, the ongoing discussion will be how to investigate and characterize Q3 for the individual dosage forms and to demonstrate the validity of Q3 measurements for BE determinations.

INTRODUCTION

There is increasing political and economic pressure to approve generic orally inhaled and nasal drug products (OINDPs) for entry to the US market. The success of OINDP generic development programs demands that the current regulatory barrier for achieving therapeutic equivalence is overcome. Demonstration of therapeutic equivalence between a proposed generic product and the RLD product, within an ANDA, requires the establishment of therapeutic equivalence through both pharmaceutical equivalence and BE [1].

Bioequivalence is defined in the 21 CFR 320.1 US regulation as "*the absence of a significant difference in the rate and extent to which an active ingredient or active moiety in a pharmaceutical equivalent becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study*" [2]. BE also plays an important role in supporting formulation changes during a new drug development phase as well as certain post-approval supplemental changes in drug applications. The rate and extent of drug absorption are usually assessed using *in vivo* PK studies in which generic and reference drug plasma concentrations are characterized and compared. However, for locally acting products such as OINDPs where the local site of action is proximal to systemic absorption, there may be little or no relevance of PK data to the drug delivery and therapeutic efficacy at the drug-receptor level [3, 4]. Determining and achieving BE for such products has proved to be a major challenge for both the pharmaceutical industry and the regulatory agencies. However, for an increasing number of locally acting drug products, well designed and validated *in vitro* approaches have been able to qualitatively predict the presence of the drug at the site of action and specifically assess its performance [5].

For OINDPs, there remain major challenges and multiple considerations in establishing BE. Since the local concentration of the delivered dose deposited throughout the nasal cavity or the respiratory airways cannot be measured directly, achieving BE between test (T) and reference (R) products is difficult. Furthermore, there is a limited understanding of the relationship between *in vitro* dosing parameters (e.g., delivered dose content uniformity, aerodynamic particle size distribution (APSD) metrics, etc.) and the actual fate of the aerosol dose *in vivo*. Due to these limitations, the FDA has adopted a "weight of evidence" approach requiring *in vitro* PK and pharmacodynamic studies to help confirm local therapeutic equivalence between test and reference OINDPs [1]. Under the Generic Drug User Fee Acts (GDUFA) initiatives, the FDA has published 17 product specific guidance (PSG) documents related to inhalation and nasal products [6]. A common theme in these PSG documents is the reliance on Q1 and Q2 sameness of the formulations and device comparability with the RLD product, together with the recommendation to establish equivalence through *in vitro* performance testing, human PK studies for the assessment of systemic exposure and clinical endpoint studies. The major barrier to both generic competition and ongoing product improvements of OINDPs is the cost and requirements for clinical endpoint BE studies. Patient numbers can be significant, sometimes larger than the originator's efficacy study. Furthermore, considering the high variability, low sensitivity, and the inability to detect formulation differences, these studies are only confirmatory of local equivalence.

To address the need to establish equivalence in local delivery, the FDA Office of Generic Drugs, through GDUFA I and II, have explored alternative pathways for these complex drug-device combination products that can reliably ensure equivalence in bioavailability without the need for a clinical endpoint BE study. The general pathway that the FDA have adopted for BE testing of locally-acting topical dosage forms applies Q3 microstructural equivalence where differences between the same components (Q1) in the same concentration (Q2) under a non-equilibrium state can be related to the arrangement of matter and/or its state of aggregation [7]. For transdermal suspensions, creams, gels, etc., if Q1 and Q2 are identical, the only potential difference between formulations is related to Q3 [7]. In contrast, for both nasal and inhaled products, the addition of a device and the variable energy source imparted by the inspiratory flow of the patient can also have a secondary influence on the structural characteristics of an aerosolized dose. This introduces the need to investigate the microstructural relationship between both formulated and aerosolized forms of the product and the influence of device and patient factors in demonstrating the validity of Q3 for bioequivalence [8].

In the 2003 FDA Draft Guidance bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action, the justification for the "weight of evidence" approach and, in particular, the need for *in vivo* clinical studies for nasal spray suspension products was due to the lack of a validated method methodology for characterizing active pharmaceutical ingredient (API)-specific particle size distribution in nasal aerosols and suspensions containing both solid active API and excipient particles [9]. However, the advent of Morphologically Directed Raman Spectroscopy (MDRS), which combines particle imaging with Raman spectroscopy in a single integrated platform, enabled structural characterization of particle size and shape, as well as chemical determination of the polymorphic form of APIs within multi-component nasal spray formulations [10]. A validated MDRS technique was used for the first FDA approval of a generic mometasone furoate nasal spray in lieu of a rejected clinical endpoint BE study [11]. The MDRS approach has also supported the submission of a nasal spray hybrid formulation in Europe. The Committee for Medicinal Products for Human Use (CHMP) commented that they "considered particle-size distribution to be an adequate indicator of dissolubility, which is, in turn, an indicator of safety and efficacy" [12].

Considering that dissolution is a prerequisite for cellular uptake and absorption in the nose and lungs, very little is known about the influence of formulation factors and local differences in drug concentration on the dissolution characteristics within an aerosolized dose. The challenge in developing a standardized *in vitro* dissolution test for inhaled products has been extensively reviewed by both the USP Ad Hoc Inhalation Advisory Panel and the IPAC-RS Dissolution Working Group [13]. The major findings of both groups were that methodologies lacked the robustness and the level of validation required for a standardized dissolution test; either as a quality control tool to assess batch consistency or for establishing *in vitro/in vivo* relationship.

This article describes ongoing developments in Q3 equivalence testing for both nasal and orally inhaled products that support an understanding of BE at the formulation level and influence on the release rate and extent of drug absorption at the site of action.

Q3 STRUCTURAL ANALYSIS OF NASAL SPRAY SUSPENSION FORMULATIONS

Commercial and Test Mometasone Furoate Monohydrate Nasal Spray Suspensions

The nasal spray suspension product Nasonex™ (mometasone furoate monohydrate) 50 μg (Lot 14MAA532A, Merck, USA) was obtained commercially and tested prior to expiration. Four test nasal suspension formulations containing mometasone furoate monohydrate were manufactured containing 0.05% mometasone using four different API batches of mometasone furoate monohydrate (Batches 1-4; Sterling, Perugia, Italy), 2% microcrystalline cellulose (MCC; Avicel® RC-591, FMC Biopolymer, Belgium). Other excipients polysorbate 80, glycerin, benzalkonium chloride, sodium citrate dihydrate, citric acid monohydrate, and purified water were also included in the formulation. All formulations were filled into white high-density polyethylene (HDPE) bottles and fitted with a screw-on VP3 pump (18/415, Aptar Pharma, France).

In Situ Particle Sizing and Morphology Analysis of Nasal Suspensions Using Morphologically Directed Raman Spectroscopy (MDRS)

The morphology and particle size distribution of both the "as received" API batches and formulated nasal suspension formulations was characterized using Morphologi G3-ID MDRS, (Malvern Instruments, Worcestershire, UK). The method development route for analysis of the as received API and nasal formulations involved optimizing sample preparation, threshold and filter setting, morphological classification of API, and excipient and chemical analysis by Raman. Before chemical analysis, the RLD nasal spray was compared with a placebo formulation which was API-free but contained excipients to identify particle morphology filters that could be used to improve the targeting of API particles during chemical analysis. MCC particles within the Nasonex product were found to be more elongated than the API and additional morphological filtering based on elongation percentages within a range of 0.3-0.5 increased the sampling of many thousands of API particles per study.

Once the filters had been applied, 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 of the same scanning area was collected using 60 second 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 particle size distribution measurements of the commercial Nasonex RLD nasal spray and the four mometasone furoate batches as-received and formulated as nasal suspension products are summarized in Table 1. The median particle size of the API in the RLD formulation was 3.20 μm and the 90% undersize was 5.47 μm.

The rank order of the PSD of the API in the test formulations was as follows: Batch 1> Batch 4>Batch 3>Batch 2. MDRS PSD measurements indicated that Batch 2 (d50% = 2.43 μm) exhibited the smallest particle size distribution. Batches 1 and 4 exhibited d50% of 5.43 and 4.21μm, respectively, with Batch 3 falling in between (d50% = 4.03 μm). For the four formulated batches, PSD measurements suggested that the particle size of the API was smaller than the input API. This may be related to changes in the size distribution due to partial dissolution and/or Ostwald ripening or manufacturing process [12]. However, the most logical reason for this difference may be attributed to the lower threshold cut-off diameter filter for the MDRS which is around the 1.5 μm limit. This limitation of the MDRS system has been addressed with the recent launch of the Morphologi 4 system (Malvern Panalytical, Malvern, UK).

Table 1.

Comparison of the particle size distribution measurements of mometasone furoate batches "as received" and within the formulated nasal suspension product.

Batches	State	$Dv_{10\%}$ (µm)	$Dv_{50\%}$ (µm)	$Dv_{90\%}$ (µm)
Nasonex (RLD)	Formulated	2.28 (0.14)	3.20 (0.92)	5.47 (1.28)
Batch 1	*As received*	*2.81 (0.05)*	*6.84 (0.50)*	*10.09 (0.48)*
	Formulated	2.72 (0.29)	5.43 (0.62)	10.26 (1.36)
Batch 2	*As received*	*1.63 (0.19)*	*2.54 (0.24)*	*3.77 (0.34)*
	Formulated	2.05 (0.01)	2.43 (0.03)	3.41 (0.15)
Batch 3	*As received*	*3.69 (0.15)*	*5.80 (0.03)*	*8.14 (0.26)*
	Formulated	2.30 (0.01)	4.03 (0.04)	6.33 (0.07)
Batch 4	*As received*	*2.60 (1.13)*	*6.54 (0.23)*	*9.72 (0.20)*
	Formulated	2.47 (0.20)	4.21 (0.46)	6.60 (0.40)

In Vitro Dissolution of Nasal Spray Suspension Formulations

The total emitted dose from a series of actuated doses of each nasal spray formulation was collected directly into an extraction cell arrangement [14], which was placed into a USP II dissolution bath. For all dissolution experiments, 3 mL aliquots were withdrawn at 2.5, 5, 10, 15, 29, 25, 30, 60, 120, 180, and 240 minute time intervals and filtered directly into high performance liquid chromotography (HPLC) vials. To maintain a constant volume in the dissolution vessel, the sampling volume was replaced with pre-warmed dissolution media. All dissolution measurements were performed at 37°C in 300 mL PBS and 0.05%w/v sodium dodecyl sulfate (SDS) media with a stirring speed of 75rpm in USP Apparatus II (Erweka GmbH, DT 126, Heusenstamm, Germany).

The *in vitro* dissolution profiles and the relationship between the first order half-life and the % of particles by volume less than 5 µm of the formulated API batches and the Nasonex RLD product are shown in Figures 1 and 2, respectively. These data suggest that there is a direct relationship between particle size of the API and the release behavior of API when tested under sink conditions. Batch 1 has the largest particle size and slowest rate of dissolution, while batch 2 has the smallest particle size, and therefore, fastest rate of dissolution. These data support the consideration made by the regulatory agencies that the rate and extent of release for local absorption of nasal spray suspensions may be indicated by particle size distribution measurements of the API within these formulated products.

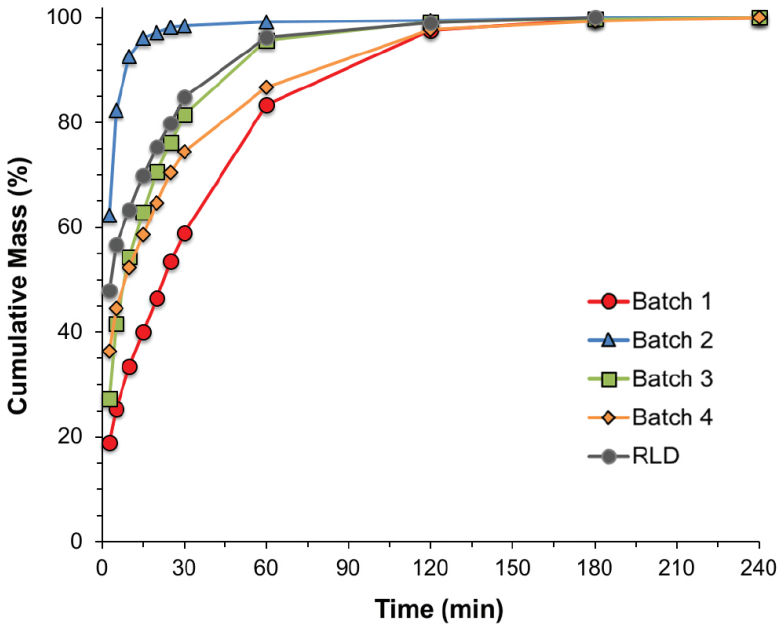

Figure 1. Dissolution release profiles of mometasone furoate from commercial Nasonex RLD and the prepared formulations with four different batches of API. Data points represent mean and standard deviation (n = 3).

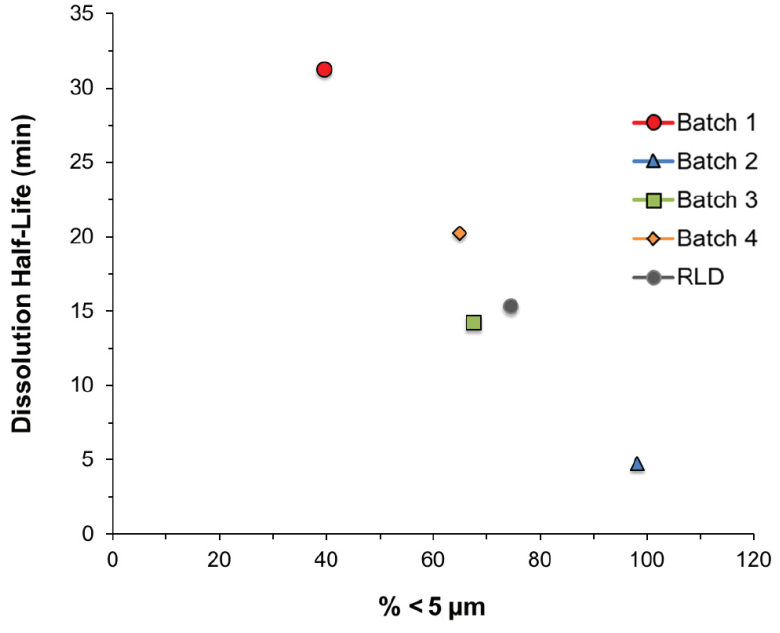

Figure 2. Relationship between the first order dissolution half-life and % of particles < 5 µm for commercial Nasonex RLD and the prepared formulations with four different batches of API.

Q3 STRUCTURAL ANALYSIS OF DRY POWDER INHALER FORMULATIONS

Commercial Dry Powder Inhaler Selection

Commercial dry powders inhalers were procured and included the Advair® Diskus® (fluticasone propionate (FP) and salmeterol xinafoate (SX) inhalation powder) 100/50 (Lot 7ZP5317), 250/50 (Lot 4ZP7006) and 500/50 (Lot 4ZP7022), and Seretide™ 100/50 Accuhaler™ ((Lot 4750), GlaxoSmithKline, Ware, UK).

Aerosol Collection Apparatus (UniDose) of the Impactor Size Mass (ISM) Dose of Orally Inhaled Product for Dissolution and MDRS

Because the dissolution techniques reviewed by USP Ad hoc Inhalation Advisory Group and the IPAC-RS Dissolution Working Group [12] have been successfully validated for topical and transdermal products, this suggested that the major limitation in dissolution studies of aerosolized drug may have been the mode of aerosol collection. To address this limitation, a bespoke aerosol collection system was designed. The UniDose system was validated for the collection of a representative lung dose for dissolution studies. The collection system uniformly deposits the whole of the impactor stage mass (ISM) across a large surface area filter which enables the dissolution release profiles to be independent of drug loading, which improves the overall ruggedness, reliability, and discriminatory capability of *in vitro* dissolution testing of OIDPs.

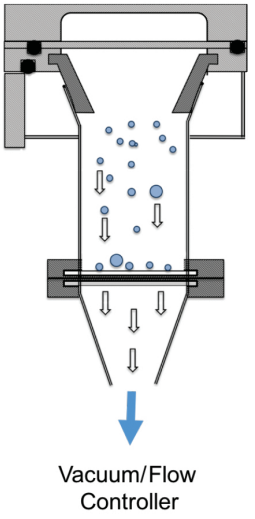

Figure 3. A schematic cross-sectional diagram of the aerosol collection apparatus (UniDose) which has been incorporated into Stage 2 of a Next Generation Impactor (NGI).

Uniform deposition of the impactor size mass (ISM) dose onto a single, high surface area filter membrane under laminar flow and low impaction velocity was achieved using the UniDose collection system. The Unidose collection system (Figure 3) was incorporated onto Stage 2 of a Next Generation Impactor (NGI) [14]. Commercial inhalation formulations were aerosolized into the UniDose system via a USP inlet port at a fixed flow rate of 60 $Lmin^{-1}$ for 4.0 seconds and collected onto a 47mm Pall A/E type glass fibre filters (Copley Scientific, Nottingham, UK).

In Vitro Dissolution of DPI Products

Dissolution profiles of orally inhaled drug products collected via the UniDose were conducted in a modified USP Apparatus V, also known as paddle-over-disk (POD) apparatus [15]. Dissolution measurements were performed at 37°C in 300 mL PBS and 0.2%w/v SDS media with a stirring speed of 75rpm in USP Apparatus V (Erweka GmbH, DT 126, Heusenstamm, Germany). The USP disk assembly membrane holder for transdermal patches was adapted to enable a 47 mm

glass fiber filter to be housed. For all dissolution experiments, 3 mL aliquots were withdrawn at 2.5, 5, 10, 15, 29, 25, 30, 60, 120, 180, and 240 minute time intervals and filtered directly into HPLC vials. To maintain a constant volume in the dissolution vessel, the sampling volume was replaced with pre-warmed dissolution media. The fractional percentage of the drug dissolved at each time point was determined by dividing the amount of drug by the total mass loading. Sink conditions were maintained during dissolution studies. Salmeterol is not dissolution limited and 100% of the dose was dissolved by the first-time point (data not shown). The dissolution data reported here focused on fluticasone propionate for all of the drug products analyzed.

Figure 4 compares the *in vitro* dissolution differences in the release profiles of FP from the EU Seretide Accuhaler (100/50µg) DPI and US Advair Diskus (100/50µg) DPI and highlight the discriminatory capability provided by the UniDose system [8]. The dissolution release profiles of the EU and US combination products were shown to be different by similarity factor (f_2) analysis [16]. The source of the differences in the aerosolized dose are considered to be structural, due to variations in the physicochemical properties of the API/excipient, manufacturing variables between different sites, packaging differences between territories, shipping and storage, or some other critical-to-quality characteristic [8].

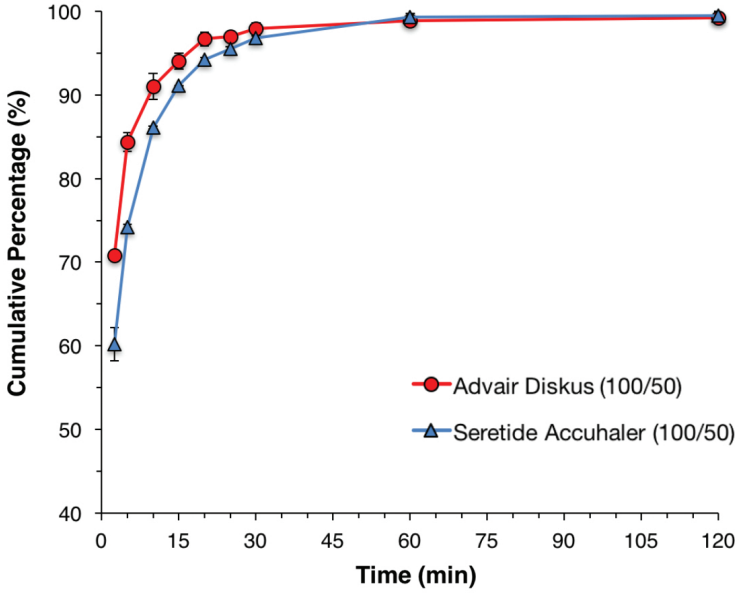

Figure 4. **USP apparatus V paddle-over-disk (POD) dissolution release profiles of aerosolized ISM dose of FP from EU Seretide Accuhaler (100/50 µg) DPI and a US Advair Diskus (100/50 µg) DPI (n = 5). Data points represent mean and standard deviation. Reproduced with permission from Reference 8.**

Figure 5 compares the *in vitro* dissolution release profiles of the FP component of the aerosolized impactor stage mass (ISM) dose of US Advair DPI Diskus 100/50µg, 250/50µg and 500/50µg FP/SX. These data suggest that the dissolution rate of the FP dose collected was inversely proportional to drug loading, in which the low strength exhibited the fastest rate of dissolution and the high strength product the slowest rate of dissolution. For a fixed concentration of SX and a constant fill weight (12.5 mg) for these unit dose blister formulations, increasing the

surface coverage of FP appears to lead to a concomitant decrease in the rate of dissolution of the aerosolized dose. Previous studies that have shown that the dissolution rate of a poorly soluble compound in an interactive mixture is inversely proportional to the degree of surface coverage and more specifically to the surface area ratio between drug and excipient [17, 18]. There is a greater likelihood of agglomerate formation over discrete drug particle-excipient interactions as drug concentration increases [19].

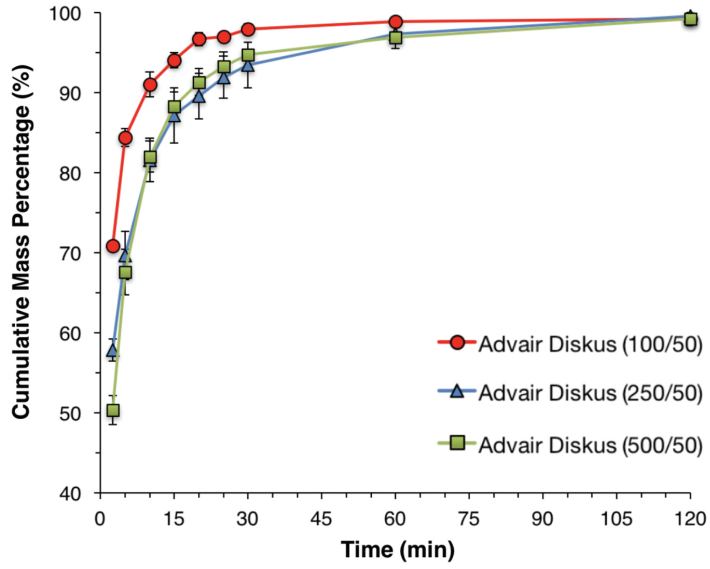

Figure 5. **USP apparatus V paddle-over-disk (POD) dissolution release profiles of aerosolized ISM dose of FP from US Advair Diskus 100/50 µg, 250/50 µg, 500/50 µg DPIs (n = 5). Data points represent mean and standard deviation. Reproduced with permission from Reference 8.**

The sensitivity in the rate and extent of dissolution of the low soluble FP compound in products from different territories and dose strengths of FP/SX fixed combination products suggest that the local drug-drug and drug-lactose interactions within the drug product may not only influence aerosol performance, but also the rate of pulmonary dissolution within the lung. It is well known for solid oral dosage forms that increased dispersion of a low soluble drug within a soluble matrix can significantly alter the dissolution rate of a sparingly soluble drug [20].

Structural Analysis of the Agglomerate Structures of Commercial RLD DPI Formulations Containing Fluticasone Propionate and Salmeterol Xinafoate

While *in vitro* dissolution studies indicated differences between commercial RLD products containing fluticasone propionate, there was insufficient evidence to fully decode the structural Q3 properties that define these product characteristics and influence product performance. Unpicking and rationalization of these properties requires other orthogonal techniques that can provide analytical information on structural interactions on a microscopic scale.

The collected ISM dose using the UniDose apparatus was also characterized using Raman chemical imaging. Upon collection, the filter substrate was mounted directly on to the sample stage of the Morphologi G3-ID. Reference spectra of fluticasone propionate, salmeterol xinafoate, and

lactose were used to identify the chemical composition of the particles collected. The scan area was set to 4.5 mm^2 and a total of 20,000 particles were analyzed for each drug product. The X-Y coordinates of the particles recorded during morphological analysis were used for locating the center of the particles, where the Raman spectrum was subsequently acquired.

The microstructural differences following MDRS analysis for the ISM dose collected from Advair Diskus 100/50 µg, 250/50 µg, and 500/50 µg FP/SX DPI products are shown in Figure 6. These data show the presence of "free-standing" or discrete API, together with mixed agglomerates within the aerosolized dose as a percentage of the total particles analysed in each case. While there are constraints associated with the spatial resolution of the G3-ID apparatus and the acquisition times needed for analysis, the Q3 map is an elegant way to compare the aerosol that would be delivered to the cascade impactor following APSD testing in each case. As shown, the percentage of discrete FP increased with increased concentration of FP in the powder blend. Moreover, the presence of FP-lactose-SX agglomerates decreased as the dose strength of FP in Advair increased. A comparison of these data with the dissolution data presented implies that the faster dissolution of FP from the US Advair Diskus 100/50 µg low dose product may be related to the smaller amount of discrete FP alongside the increased FP agglomeration with more soluble components, lactose, and SX, that could accelerate FP dissolution. The slower rate of dissolution of FP from both the mid- and high-strength formulations was consistent with the increased amount of freestanding FP (Figure 6) and lower volume of mixed agglomerate structures, resulting in poor wettability of FP and a reduction in dissolution rate. These data support the role that both *in vitro* dissolution testing of sparingly soluble compounds and microstructural characterization by MDRS may play in enabling scientifically valid measurements of the state of aggregation of APIs within a representative lung dose.

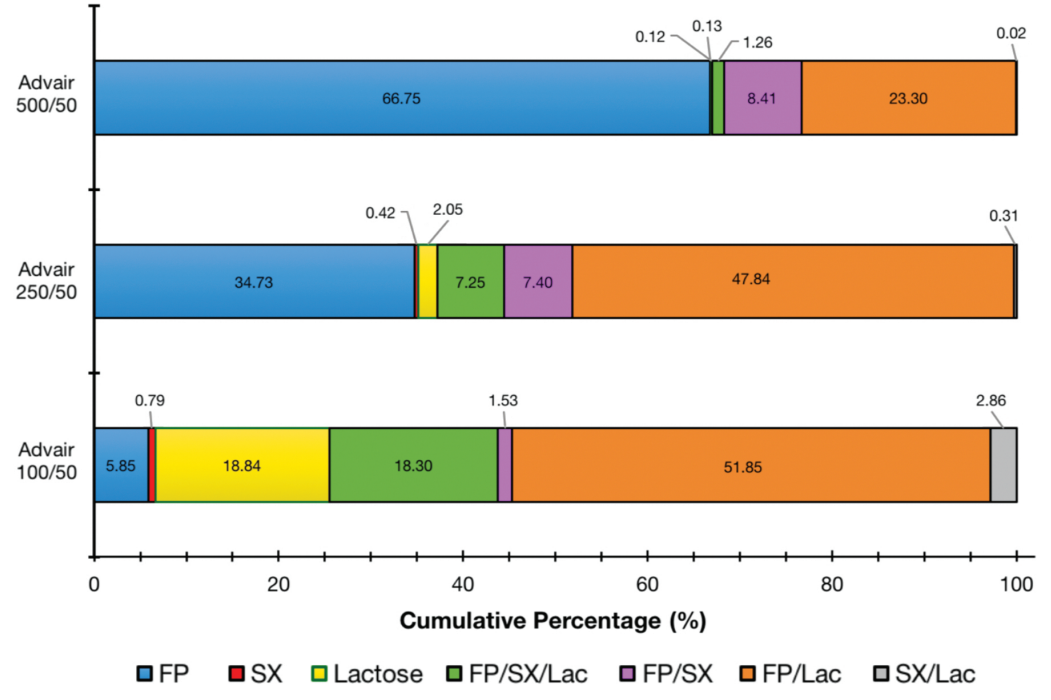

Figure 6. **MDRS structural analyses of the state of agglomeration as a percentage of the total number of particles analysed as either freestanding FP or agglomerated with lactose, SX, and SX-lactose from US Advair Diskus 100/50 µg, 250/50 µg, 500/50 µg DPIs. Reproduced with Permission from Reference 8.**

CONCLUSIONS

The concept of Q3 structural equivalence for OINDPs has been introduced to improve both the scientific understanding of the fate of the dose delivered locally intranasally or to the respiratory tract. By using advanced *in vitro* and *ex vivo* techniques, such as dissolution testing and MDRS, together with validated *in silico* mechanistic modeling, alternative approaches for inter-product comparisons may become possible. Further research is needed to identify and validate the optimal methods to investigate and characterize Q3 for nasal and inhalation products for BE determination.

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