How critical quality attributes of the drug substance can support orally inhaled and nasal drug product (OINDP) quality

Case studies on particle characteristics, including morphic form, particle shape and surface characterization are presented.

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The US regulatory framework for bioequivalent OINDPs

Since the implementation of the Generic Drug User Fee Act (GDUFA) in 2012, the United States Food and Drug Administration (FDA) has established enhanced regulatory pathways and specific product development guidance with the goal of facilitating generic drug product availability and expanding access to high quality and affordable medicines for the public. Orally inhaled and nasal drug products (OINDPs) have benefited from these significant advances in regulatory-science frameworks, which identify appropriate methodologies for generating evidence to support new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for these complex drug/device combinations.

At the Complex Generic Drug Product Development Workshop held in September 2019, the FDA reported that 46 product-specific guidances (PSGs) were available for OINDPs (nasal solutions and suspensions, metered dose inhalers and dry-powder inhalers) [1]. In June 2020, the FDA announced plans for new and revised product-specific guidances that included 12 additional OINDPs. These PSGs for complex drugs should help de-risk and improve the efficiency of generic drug development by leveraging the scientific understanding and increasing regulatory clarity for products where competition is lacking. Even so, OINDPs continue with limited or no generic alternatives in the US market and can remain expensive to develop due, in part, to the FDA's current pathways for establishing bioequivalence (BE) for OINDPs based on the aggregate weight-of-evidence, which requires comparative clinical pharmacodynamic (PD) endpoints in addition to pharmacokinetic (PK) and *in vitro* studies [2].

Evolving scientific standards in the development of OINDPs

Research sponsored by the FDA during the last eight years has been focused, in part, on establishing scientific standards and increasing the science about bioequivalence by determining *in vitro/in vivo* correlations (IVIVC), by looking into new and emerging technologies for analytics and manufacturing, and by adding advanced analytics (instrumental and modeling) to development requirements [3]. For OINDPs, in which the drug substance is in suspension rather than in solution, such research has been centered on the physicochemical properties of the drug substance. In particular, particle morphology and microscopy-measured size have been considered important product quality attributes, providing scientific information that supported PSGs and general guidances. For example, recent revisions to PSGs for nasal suspensions (budesonide, azelastine hydrochloride and fluticasone propionate, mometasone furoate monohydrate and triamcinolone acetonide) include, for the first time, alternative language about approaches to bioequivalence that is based on adequate characterization of the drug substance particle size distribution, supported by comparative particle characterization using advanced analytical techniques.

The FDA's Draft Guidance for Industry, "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations" released in April 2018, discusses quality attributes for metered dose inhalers (MDIs) and dry powder inhalers (DPIs) [4]. Regardless whether pursuing innovator or generic product development, the importance of establishing a desired quality target product profile (QTPP) is highlighted, in order to define the characteristics of the drug product that ideally will be achieved to ensure the desired quality. Further, it is recommended that the applicant, from the earliest stages of development, develop a list of critical quality attributes (CQAs) to ensure such desired product quality. For drug substances, potential product CQAs typically include assay, particle size distribution, moisture content, bulk density, flow properties, morphic form (e.g., amorphous, crystalline, hydrate), morphology of drug particles (e.g., shape, crystal habit, texture, surface area, rugosity), residual solvent content and impurities. These attributes can relate to the performance of an OINDP during various processes, as shown in Table 1.

Only after considering all of these properties, should the drug product developer focus on risk assessment, regarding clinical material attributes (CMAs) and clinical process parameters (CPPs), in order to define a design space and a control strategy for life cycle management. These characterization methods play an important role in helping ensure that a robust process exists for product quality control, thereby assisting in gaining approval from the regulatory agency.

Case studies

The following sections of this article present case studies. As typical CQAs of drug substances for OINDP applications are numerous, these studies are not intended to address all possible attributes. Instead, they focus on the most common particle characteristics, including morphic form, particle shape and surface characterization. The analytical techniques chosen were X-ray powder diffraction (XRPD), scanning electron microscopy (SEM), particle surface area by Brunauer-Emmett-Teller method (BET), surface energy by inverse gas chromatography (IGC) and particle size distribution (PSD) by laser diffractometry (LD). Characterization results for fluticasone propionate (FP), fluticasone furoate (FF), vilanterol trifenatate (VT) and/or salmeterol xinafoate (SX) powders, micronized by jet milling and/or wet polishing, as well as various process parameters for the techniques, are discussed.

Jet milling (JM) is the particle size reduction process most used in the pharmaceutical industry to obtain powders within the inhalation size range. During this process, the powder to be size-reduced is fed into a milling chamber where compressed air or nitrogen, usually in a vortex motion, promotes particle/particle collisions. Particle classification is made by differing inertia, following reduction via impaction and abrasion. Jet milling is a solvent-free and cost-effective technique capable of yielding an appropriate PSD for inhalation applications and can be used with heat-sensitive materials. However, the high input energy needed can promote amorphization, change in morphology and chemical degradation of the material [6]. The surface of the crystal can become damaged and local "hot spots" (localized areas of

Table 1

Potential impact of drug substance quality attributes on processing behavior (adapted from [5]).

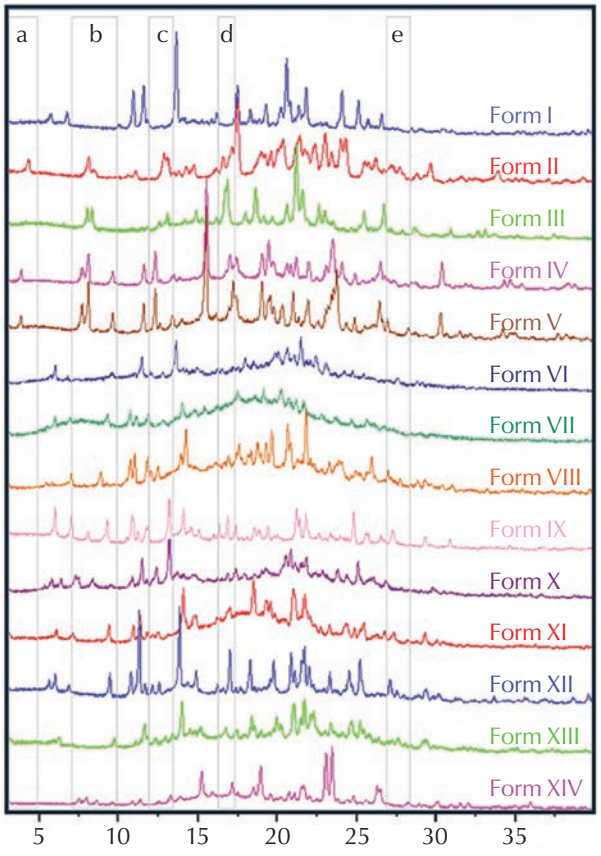
	Flow	Blending	Wetting	Drying	Dissolution	Stability
Particle size distribution	+	+	+	+	+	+
Morphology	+					
Amorphous content			+		+	+
True density				+		
Bulk density	+		+			
Surface area	+	+	+	+	+	+
Surface energy	+	+	+			
Flowability	+					
Cohesiveness	+	+				
Static charge	+	+				

extremely high temperatures and pressures) can be generated [7]. These sites can promote the formation of amorphous domains and a modification in the polymorphic form of the drug substance. The resulting particles can be highly electrostatically charged and result in fractured crystals. The increase in the particle surface energy can also lead to greater cohesive behavior between drug particles and/or among drug and excipient particles [6]. During jet milling, control of particle size, shape and morphology can be limited [8-10].

Wet polishing (WP) is a wet-milling technique (patented by Hovione) that can generate stable crystalline material. This technique uses an anti-solvent to produce a suspension during the milling phase, which is later removed during a subsequent drying step (e.g., spray drying) [11]. The wet-polishing process is easily scalable and has the advantage of offering very high control over particle size distribution, enabling finer PSD customization with narrower spans. The energy applied during the process is largely dispersed to the liquid, decreasing stress in the particles and consequently reducing amorphization of the particles. Nevertheless, the process requires a suitable anti-solvent that does not dissolve the particles and/or change the chemical properties of the drug substance and also requires an isolation step. This could be challenging for thermally unstable compounds [6].

Figure 1

XRPD diffractogram of crystalline profiles (forms) I to XIV for vilanterol trifenatate [18-19].



Drug substance particle crystallinity and polymorphism

For OINDPs, the solid form of the drug substance will strongly impact the formulation in achieving the required bioavailability, physical properties and stability [12-13]. These characteristics are important for equivalent or innovative efficient administration of the drug substance, to ensure that an effective dose is consistently delivered to the correct region of the respiratory tract and that, once deposited, the drug is effective in treating diseases.

The crystalline state of a material is associated with a specific crystal habit. The majority of pharmaceutical manufacturing processes comprise a sequence of crystallization processes in order to achieve higher purity and the desired crystalline form. However, the various solvents and processing conditions utilized in the sequence of a crystallization process may modify the crystal habit of the purified drug [14-16]. The crystalline state will influence the physicochemical properties of the drug substance such as solubility, dissolution rate, melting point and particle size.

The performance of the drug product, related to flow capability, compressibility and wettability, can be optimized by changing the crystal habit and form of the drug substance [17]. The desired crystal form of the drug substance can be associated with different polymorphs of the pure drug substance but also with other types of structures such as solvates, hydrates, salts or co-crystals [13]. For example, in considering vilanterol trifenatate (VT) as the drug substance of interest, several novel polymorphic forms were obtained corresponding to solvated and hydrated structures [18-19].

These crystalline forms are identifiable as distinct from profile I (also called form I) of the reference listed drug (RLD) because they show different characteristic peaks in XRPD diffractograms (Figure 1). These differences are identified by their characteristic diffraction angles (2θ), which fall within, or at each end of, one or more of the following sub-ranges: (a) 3-5°, (b) 7-9.9°, (c) 12-13.3°, (d) 16.4-17.3° and (e) 26.8-28.3°, also identified in Figure 1.

These polymorphs can provide benefits over profile I due to their potential use in medicine for the same or similar conditions as those treated with vilanterol trifenatate. This is due to the enhanced purity, variable hygroscopicity, solubility and degradation temperatures that can be adapted for use [19].

In a second example, involving fluticasone propionate (FP) particles, an XRPD analysis investigated the influence of micronization on the crystallinity and polymorphism of the materials produced. This evaluation for the presence of different polymorphs is

very important to assure equivalence between the reference listed drug and the produced drug substance as well as to evaluate the formulation stability [20].

It was possible to conclude that the micronization technique did not significantly alter the degree of crystallinity or the polymorphic form of the particles whose diffractograms are shown in Figure 2a. Both samples present similar sharp diffraction peaks at the same 2θ angles, indicating the two drug substances did not alter their polymorphism during the micronization processes. As explained previously, the high input energy needed in jet milling can promote amorphization. Nevertheless, by adapting the operating conditions (pressure and feed rate), it was possible to overcome the risk of amorphization and create fully crystalline materials. Similar equivalence was observed for other drug substances micronized by both techniques, for example, salmeterol xinafoate (SX in Figure 2b) and fluticasone furoate (FF in Figure 2c), where diffractograms from wet-polished and jet-milled powders show superimposed XRPD profiles.

Particle shape

Alternative milling processes may be an advantage in developing innovative formulations because these micronization technologies can be used to fine-tune the drug substance particle's physical properties, such as its shape, according to the formulation and application. In the example presented in Figures 3a, b and c for fluticasone propionate (FP) powder particles, particle shapes that were observably different in scanning electron microscopy could be obtained simply by adjusting the operating parameters of the jet-milling technique.

Needle-shaped particles were obtained for jet-milled FP1 (FP1 JM in Figure 3a) while plate-like shapes were formed for jet-milled FP2 (FP2 JM in Figure 3b). The difference between these samples was in their process parameters (pressure and feed rate) and as can be seen, the milling process strongly impacts the particle surface properties including shape [21]. Further, the surfaces of both drug substances produced by jet milling were more wrinkled when compared to surfaces of wet-polished FP1 (FP1 WP

Figure 2

XRPD diffractograms for a) fluticasone propionate (FP), b) salmeterol xinafoate (SX) and c) fluticasone furoate (FF), micronized by jet milling (JM) and wet polishing (WP).

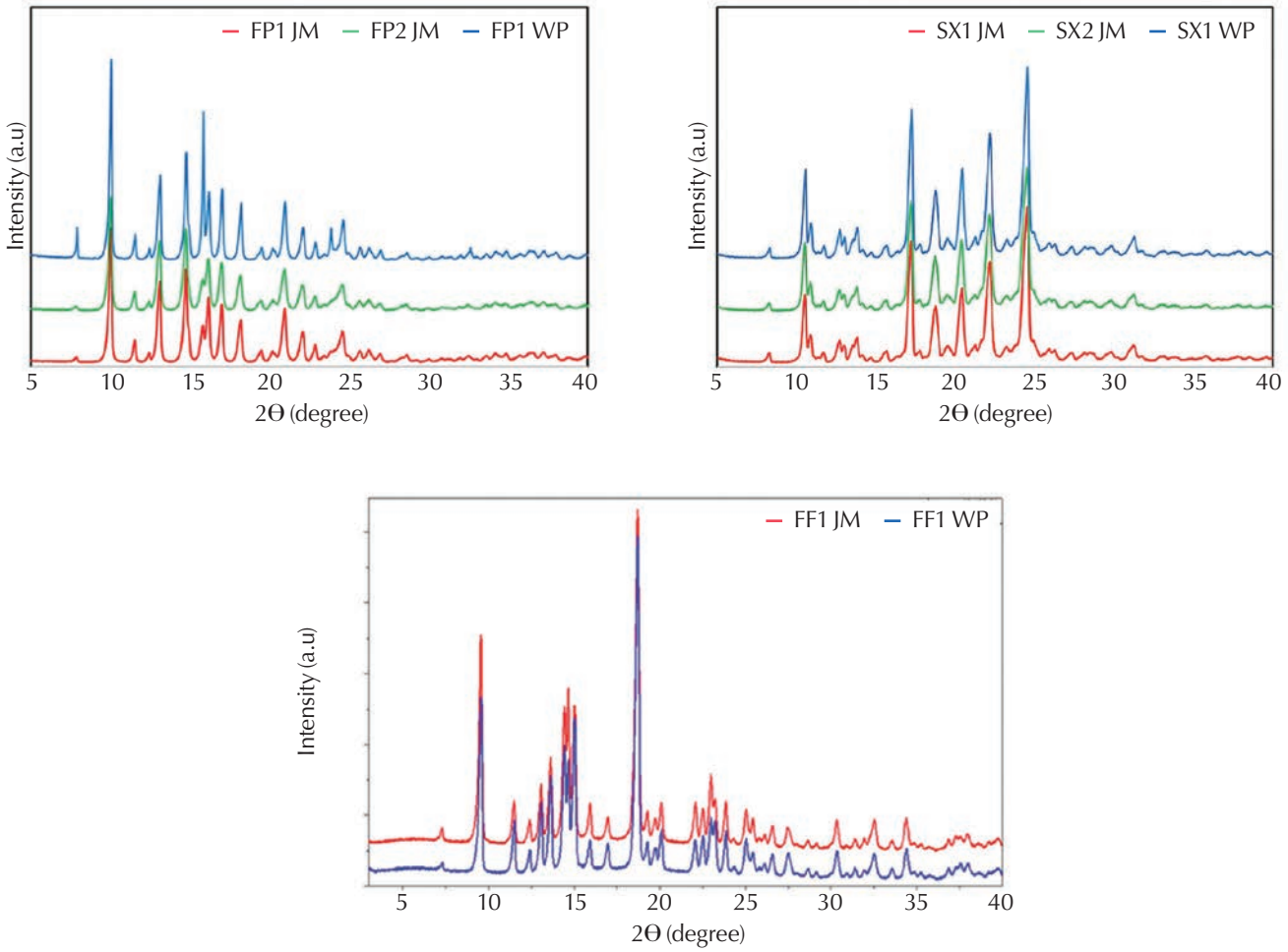


Figure 3

SEM images for a) FP1 JM, b) FP2 JM, c) FP1 WP, d) SX1 JM, e) SX2 JM, f) SX1 WP, g) VT1 JM, h) VT1 WP and i) VT2 WP.

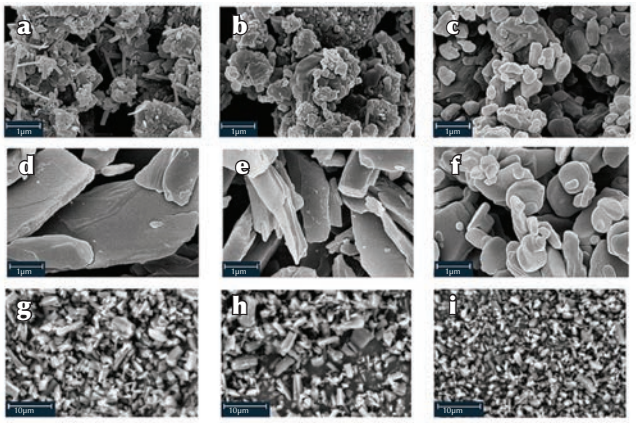


Table 2

Particle size distribution and specific surface area results for FP, SX and VT micronized by jet milling (JM) and wet polishing (WP).

Drug Substances	Particle size distribution (µm)				Specific surface area (m^2/g)
	D_{10}	D_{50}	D_{90}	Span	
FP1 JM	1.1	2.8	6.7	2.0	9.3
FP2 JM	1.1	2.6	5.0	1.5	12.7
FP1 WP	0.6	2.0	5.1	2.3	6.3
SX1 JM	0.9	2.5	5.3	1.8	3.5
SX2 JM	0.7	1.8	3.6	1.7	5.7
SX1 WP	0.6	1.5	3.2	1.7	4.3
VT1 JM	1.3	2.3	4.2	1.3	3.9
VT1 WP	1.0	2.3	4.7	1.6	3.6
VT2 WP	0.7	1.5	4.0	2.2	9.3

in Figure 3c). Wet polishing produced noticeably smoother-surfaced particles because, in this two-step milling process, the applied energy is highly dispersed in the liquid, thereby decreasing stress in the particles and producing polished surfaces.

Higher surface roughness results in increased particle/particle separation and thereby reduced contact surface. This contact surface may be between individual drug particles or between a drug particle and the carrier particle surface, where larger carrier particles are present in the formulation. In the latter case, the overall effect is to reduce the adhesion of drug substance particles to such surfaces [22].

The particles of salmaterol xinofoate micronized by jet milling (Figure 3d and e) have more surface irregularities, with sharper edges, than particles of the same drug substance micronized by wet polishing (SX1 WP). The latter are closer to being spherical, having smoother, rounded surfaces (Figure 3f), which correlates with the example for fluticasone propionate discussed previously. This can be beneficial, depending on the formulation process [23].

Finally, in the case of vilanterol trifenatate (Figures 3g, h and i), the particle shapes are very similar between the drug substance produced by jet milling and by wet polishing. In this case, the physicochemical properties of the starting raw material (density, particle size and particle shape) are such that differences in the energy applied for both processes will not significantly alter the final products.

The shape and size of the processed particles are directly related to their surface area (see surface characterization section) and to particle/particle surface interaction. On a microscopic scale, such considerations affect the cohesive/adhesive balance (CAB) between adjacent particles in the bulk powder, and consequently, its flowability during formulation processing and, subsequently, the aerodynamic behavior upon aerosolization when the patient inhales the commercially available drug product. [9] Other analytical techniques can be employed to improve evaluation of these parameters, for example Atomic Force Microscopy (AFM) [24-26], but this topic is beyond the scope of the present article.

Surface characterization

Spray droplet/solid particle size CQAs directly influence clinical efficacy [9]. Apart from the spray particle size distribution during formulation development, the drug substance particle size distribution within the dispersed aerosol also plays an important role, defining the efficacy of drug delivery as well as overall bioavailability [26]. This is critical for both innovator drug product and generic drug product development, during pre-formulation studies to understand the reference listed drug characteristics, and in particular for nasal sprays, to allow the use of *in vitro* bioequivalence studies. [27]

Aerodynamic particle size distribution (APSD) is a major determinant in deposition and distribution of the drug substance within the lungs. Particles deposit in the respiratory tract by inertial impaction, sedimentation and diffusion. To reach the lower respiratory tract (past the trachea), the majority of the inhaled particles should be less than 5 µm in aerodynamic diameter [28-31].

The microscopy-measured geometric particle size of the drug substance particles, also often determined rapidly by laser diffractometry, is inversely propor-

Table 3

Dispersive component of surface energy (γ_s^d, mJ m^{-2}) and specific component of work of adhesion (W_a^s, mJ m^{-2}) for polar probes (Lewis acid/base).

Drug Substances	γ_s^d (mJ m^{-2})	W_a^s (TCM)	W_a^s (DCM)	W_a^s (THF)	W_a^s (DIE)	W_a^s (Acetone)	W_a^s (ETA)	W_a^s (THF)/ W_a^s (TCM)	W_a^s (DIE)/ W_a^s (TCM)
VT1 JM	35.8 ± 2	3.8 ± 0.0	3.0 ± 0.0	10.2 ± 0.0	8.3 ± 0.2	16.3 ± 0.2	10.5 ± 0.1	2.7	2.2
VT1 WP	32.9 ± 2	1.5 ± 0.0	0.5 ± 0.3	9.5 ± 0.7	7.0 ± 0.0	15.8 ± 0.2	9.7 ± 0.2	6.5	4.8
FP2 JM	53.0 ± 2	1.4 ± 0.7	9.3 ± 0.6	23.1 ± 0.4	21.3 ± 0.2	40.6 ± 0.6	---	16.5	15.2
FP1 WP	52.5 ± 2	3.0 ± 0.7	6.5 ± 1.0	21.7 ± 1.0	19.4 ± 0.3	36.7 ± 0.5	---	7.2	6.5

tional to the specific surface area (SSA). The specific surface area, usually measured by a gas adsorption method, depends on both the particle size distribution and surface roughness. Smaller particles show larger specific surface areas and larger particles show smaller specific surface areas, assuming equivalent and micro-/meso-/macro-pore distributions [32]. Pore sizes can be classified depending on their size; pores with a diameter below 2 nm are classified as micropores, between 2 to 50 nm as mesopores and above 50 nm as macropores [33].

The consistent control of all of these attributes is important to assure good control during the formulation process, with consistent interaction between the drug substance particles and excipients (and/or other materials present in the final product) as well as good control of the material properties, including dissolution and flowability [34].

In the first example (data presented in Table 2), for the three drug substances of interest, the nitrogen gas specific surface area of milled powders was obtained using a Micromeritics ASAP 2000 analyzer (Micromeritics, Norcross, Georgia, US). This technique determines the surface area of powders by monolayer gas adsorption using the Brunauer-Emmet-Teller theory. The BET theory assumes that the adsorption energy is independent of the adsorption sites and that gas molecules interact only in the vertical direction; lateral interactions between adjacent adsorbed molecules are considered negligible [33].

Particle size distribution was measured (n = 3 consecutive replicates) by laser diffractometry using a Malvern Mastersizer 2000 (Malvern, UK) with a Hydro S wet dispersion unit. With exception of jet milling for vilanterol trifenatate (VT JM), these techniques were the validated methods specific for each commercial drug substance, in accordance with ICH guidelines [35].

Comparing the results of the SSAs for the same drug substances produced by different milling processes (FP2 JM with FP1 WP; and SX2 JM with SX1 WP), the particles micronized by wet polishing had smaller values for SSA. This outcome was expected, based on the smoother surfaces of the wet-polished formulations observed from the SEM images previously described. Furthermore, comparing the SSA results for the same drug substance produced by jet milling but with different PSDs (FP1 JM with FP2 JM; and SX1 JM with SX2 JM), the smaller particles were associated with larger specific surface areas, as expected.

For the VT drug substance, since the particle roughness and morphology of the powders produced by both milling methods are similar, it can be observed that for a certain PSD (VT1 JM and VT1 WP), the specific surface area is also very similar. By decreasing the PSD, the specific surface area increased exponentially.

The second example of surface characterization relates to surface energetics studied by inverse gas chromatography. This analytical method is sensitive only to the material surface and, in particular, to the highest-energy sites of the surface. IGC is a vapor probe technique applicable to powders and fibrous materials and allows assessment of the drug substance porosity, irregular surface topographies and surface heterogeneity, making it an attractive characterization tool for pharmaceutical powders [34].

In this example, the IGC analysis was performed in a DANI GC 1000 digital pressure control gas chromatograph (DANI Instruments, Cologno Monzese, Italy). The samples were packed on a stainless-steel column and analyzed at approximately 50 °C. The substances injected were methane, n-pentane, n-hexane, n-heptane, n-octane, trichloromethane (TCM), dichloromethane (DCM), tetrahydrofuran (THF), diethyl ether (DIE), ethyl acetate (ETA) and acetone. The experiments were conducted at infinite dilution conditions following Henry's Law, where the amount of probe molecules adsorbed is linearly dependent on the injection concentration [36].

IGC enables determination of multiple surface parameters but this example focused on the dispersive component of the surface free energy (γ_s^d) and Lewis acid/base specific components. The dispersive component of the surface free energy is related to long-range interactions, in particular Van der Waals forces, while the Lewis acid/base properties of the surface were evaluated by calculation of the specific component of work of adhesion (W_a^s)with the use of polar solute molecules [36-37].

The dispersive surface energy was found to be independent of the milling process employed for both drug substances, VT and FP, and was characteristic of the material, as shown in Table 3. Nevertheless, the specific component that relates to the work of adhesion for polar probe molecules tetrahydrofuran, trichloromethane, dichloromethane and diethyl ether gives some insights about the acid/base character of the material surface produced by different milling processes.

In general, the jet-milled powders have higher values of work of adhesion for both acidic and basic probes, while the wet-polished powders are less charged. This was interpreted as being inherent to the milling process where the energy is dispersed in the liquid during wet polishing.

The main difference between the powders produced by the two milling processes is the result of the work of adhesion with the acidic probes (TCM and DCM), which reflects in different ratios: W_a^s (THF)/W_a^s (TCM) and W_a^s (DIE)/W_a^s (TCM). In both cases, these ratios are positive, which corresponds to a larger number of highest-energy acidic sites or to potential higher acidic interactions [36]. Nevertheless, the VT produced by wet polishing had a larger number of highest-energy acidic sites relative to that of highest-energy basic sites, while for FP this was observed for the jet-milled powder. This was interpreted as being the result of the different solvents used in wet polishing for both drug substances and as being inherent to the material itself.

In the case of FP, the specific component of work of adhesion for the ETA probe could not be measured due to its strong interaction with the powder samples and was associated with a very long retention time. Both powder samples showed a stronger interaction with the amphoteric probe (acetone), suggesting an amphoteric behavior, coupled with a higher affinity to basic probes (THF and DIE), thereby revealing an acidic character [38].

Discussion

This article highlights various ways key physical properties of drug substance particles, exemplified by FP, SX and VT powders, might be adjusted and measured in order to meet a QTPP, either by using different particle size reduction techniques or by adjusting the process parameters for those techniques.

Early characterization of drug substances can provide useful insights for developers and manufacturers of OINDPs and may thereby improve a formulation process, potentially reducing development time and costs.

Advanced particle characterization of drug substances and the design of the crystallization and particle-reduction processes to deliver consistent particle morphology with respect to shape, PSD, surface properties and crystallinity is a regulatory expectation for NDA and ANDA applications for nasal suspensions, suspension metered dose inhalers and dry powder inhalers. Recently published FDA guidance documents relating to generic products augment the range of conventional analytical techniques described in Chapter <5> of the United States Pharmacopeia [39].

As a QTTP is established, discussions between the supplier of the drug substance and the drug product developer/manufacturer can provide valuable insights that may assist in increasing speed of development, improving the quality of NDA and ANDA applications and decreasing development costs. In addition, use of new development approaches, such as those presented in this article, may help increase consistency in processing.

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