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RESEARCH PAPER

Effect of Humidity on Aerosolization of Micronized Drugs

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ABSTRACT

The variation of aerosolization with humidity for three micronized drugs used in the treatment of asthma was evaluated by using in vitro methods. Micronized samples of disodium cromoglycate (DSCG), salbutamol sulphate, and triamcinolone acetonide (TAA) were stored for 12 hr at 15, 30, 45, 60, and 75% relative humidity (RH). A suitable ''reservoir'' dry powder inhaler was loaded and tested by using a twin-stage impinger at each specific humidity. The aerosolization efficiency of all three micronized drugs was affected by variations in humidity. The percentage of the delivered dose and the fine particle fraction of the loaded dose (FPF_{LD}) for both DSCG and salbutamol sulphate decreased with increasing humidity; with the largest decrease in FPF_{LD} occurring between 45% and 60% RH for DSCG and 60% to 75% RH for salbutamol sulphate. These observations suggest that the adhesion properties for both DSCG and salbutamol sulphate, which govern the aerosolization efficiency, are predominately influenced by capillary interactions. In contrast, the FPF_{LD} for TAA significantly increased as the humidity increased over the range 15% to 75% RH, suggesting that triboelectric forces predominate particle-particle interactions. These variations in drug particulate behavior highlight the importance of an individual formulation approach when developing dry powder inhalation systems.

Key Words: Dry powder aerosolization; Humidity; In vitro.

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INTRODUCTION

A range of antiasthmatic drugs are currently available in the form of micronized dry powders for inhalation, each presenting a unique formulation challenge. The fine particle dose delivered by a dry powder inhaler (DPI) is directly related to the sum of the forces acting between the powder particulates and the effectiveness of the aerosolization mechanism at overcoming those forces.

The interactions between powder particulates are governed by a composite of van der Waals, electrostatic, and capillary forces. The magnitude of each of these forces is determined by material properties and local environmental conditions, such as temperature and relative humidity (RH).[1] These factors are especially important in DPIs because micronized powders have a high specific surface area making them particularly susceptible to interparticulate forces.

At lower RHs, electrostatic forces can become a predominating factor in particulate interactions. These electrostatic forces are a result of an equilibration of different energy states between two contiguous surfaces (contact electrification). Since drugs used in inhalation tend to be organic and, therefore, act as insulators, multiple contacts between particulates during handling and aerosolization can result in triboelectric charging.[2,3] These interfacial charges can result in an increase in attractive forces between micronized materials, leading to an increase in contact area and, thus, potentially causing a greater degree of cohesion. However, in the presence of moist air, water can adsorb onto a materials surface,[1] allowing mobilization of surface electrons, increasing surface conductivity, and subsequently reducing specific charge.[4]

At higher RHs, capillary forces dominate interparticulate interactions. The presence of adsorbed water on the surface of powders causes attractive forces due to the capillary action of adsorbed water layers. At higher humidities, water vapor can condense in the capillaries, which exist between individual powder particulates, forming liquid bridges.[1,5] The presence of liquid bridges will increase the cohesive forces between particulates, resulting in an increase in tensile strength.[6] In extreme cases, where highly soluble materials are present, dissolution and subsequent solidification of the particulate surfaces can lead to the formation of solid–liquid bridges, increasing particle size and decreasing the fine particle fraction (FPF).

These observations suggest in vitro aerosolization performance of dry powder inhalers may be affected by relatively small changes in humidity. Recent investigations[7,8] have shown that storage of a variety of micronized salbutamol salts in relatively high humidities for short periods (3–60 min) resulted in an apparent decrease in the relative amount of FPF ($< 6.4\,\mu m$). In addition, studies describing the relationship between drug aerosolization and humidity reported similar effects for disodium cromoglycate (DSCG).[9,10] However, these investigations concentrated on the aerosolization of DSCG from larger carrier materials and, therefore, were not specific to the drug-drug interactions.

The effect of environmental conditions on the interparticulate forces, and subsequent aerosolization performance, will be drug specific signifying the requirement for an individual formulation approach. The need for such an approach is demonstrated here.

A comprehensive investigation was undertaken to evaluate the effect of humidity on the aerosolization of a series of micronized drugs. Three micronized drugs, of comparable particle sizes, were chosen for investigation: salbutamol sulphate, whose formulation is generally regarded as relatively straightforward; DSCG, a hygroscopic powder; and triamcinolone acetonide (TAA), a material recognized for its electrostatic charging during handling and processing. A series of in vitro aerosolization investigations of each micronized drug were conducted while contained within a environmental humidity test chamber. In contrast to previously reported studies,[7–10] this study focused on the investigation of drug-drug interactions after relatively long storage times (12 hr) at a variety of specific humidities.

MATERIALS AND METHODS

Materials

Micronized salbutamol sulphate, micronized DSCG, and micronized TAA were supplied by Aventis Pharma (U.K.). All solvents and chemicals were of at least analytical grade and were sourced from BDH (Poole, U.K.).

Physical Characterization

Particle size analysis was determined by laser light scattering (Mastersizer 2000; Malvern Instruments, Worcs, U.K.), using a large volume circulating sample dispersion cell. Approximately

100 mg of powder was suspended in a 0.1% weight by volume (w/v) lecithin cyclohexane solution and ultrasonicated for 5 min at 25°C prior to analysis (experimentally determined to be sufficient to fully deagglomerate each powder). Fifty percent cumulative undersize ($d_{0.5}$) median diameters were calculated and corrected for refractive index by using best-fit algorithm software.

Due to the hygroscopic nature of pharmaceutical powders, surface morphology was investigated by using cryogenic low-temperature scanning electron microscopy (LTSEM) (Jeol 6310; Jeol, Japan), using a method described elsewhere.[11] The effect of humidity on the particle morphology also was investigated by using LTSEM, after storage of the powders in a tightly sealed container containing a saturated solution of sodium chloride (75% RH) for 12 hr.

Density measurements were determined by using helium pycnometry (Accupyc 1330 Gas Pycnometer; Micrometrics, Norcross, GA). Samples were prepared by drying in open pans at 40°C for 24 hr prior to analysis. The temperature was maintained at 27°C during outgasing and analysis. X-ray diffraction spectra of DSCG, salbutamol sulphate, and TAA at approximately 15, 45, and 75% RH were obtained by using an x-ray powder diffraction system connected to an enviromental control unit (D5000; Bruker, Cheshire, U.K.).

Equilibration water content of each of the micronized drugs was determined by storing small samples (< 100 mg) of micronized materials (as supplied) in tightly sealed containers, together with different saturated salt solutions for 12 hr. Saturated salt solutions of lithium chloride (11% RH), calcium chloride (29% RH), potassium carbonate (43% RH), sodium permanganate (63% RH), sodium chloride (75% RH), and potassium chloride (84% RH) were used.[12] Phosphorous pentoxide was used to produce a moisture-free environment. Each powder was then weighed accurately and analyzed for total water content ($n = 3$) by Karl Fischer titration (MKC-510E; Kyoto Electronics, Tokyo, Japan).

In Vitro Characterization

All testing was conducted inside an environmental test chamber, (Termarks 6350; Copley Instruments Ltd. Nottingham, U.K.) capable of maintaining an environment of 10–95% RH (±0.2% RH) at 25°C. The aerosolization of the drug powders was investigated by using apparatus A (British Pharmacopoeia), the twin stage impinger (TSI) (Copley Instruments Ltd, Nottingham, U.K.), containing 7 mL of dilution solvent in stage one and 30 mL of dilution solvent in stage two, which at 60 L min^{-1} produces a cutoff mass median aerodynamic diameter of 6.4 μm between the two stages.[13] Prior to testing, a 60 L min^{-1} flow rate through the TSI was set by using a dummy Turbohaler™ (Astra-Draco AB, Lund, Sweden).

Approximately 20 mg samples of the micronized drugs were stored on open pans at the analysis humidity, in the environmental chamber, for a minimum of 12 hr prior to loading. This was experimentally determined as a sufficient time to allow the micronized drug powders to reach equilibration moisture content. Approximately 1500 μg of the humidity-equilibrated micronized drug was precisely weighed onto the plastic metering disk of a modified DPI Turbohaler,[14] containing no desiccant. The DPI and assembled TSI were equilibrated at the test conditions for a further 60 min prior to analysis. The loaded DPI was inserted into a specially constructed mouthpiece and tested at 60 L min^{-1} for five sec by using a solenoid valve timer (Copley Instruments Ltd. Nottingham, U.K.). A three sec delay prior to testing was instigated to allow the pump time to settle. The deposited drug fractions were collected from the DPI and TSI stages by using a suitable wash solvent and were analyzed by using high-performance liquid chromatography (HPLC) (Waters Alliance, Waters Ltd, U.K.). Drug content remaining in the DPI device was collected by carefully deconstructing the device components and washing separately with solvent. The device components were then rinsed with distilled water, followed by methanol, and dried at 40°C in an oven. The DPI components were then left to cool, reassembled, and reused. No apparent degradation in component parts or device integrity was observed by conducting this procedure. A similar water-methanol rinsing procedure was used for the TSI.

Drug content collected from the device, TSI throat/mouthpiece adapter, stage 1 and stage 2, were calculated against a series of bracketed standards by using HPLC and expressed as a percentage of the total recovered dose (or loaded dose). Analysis of the mass balance between the "weighed" loaded and total recovered dose showed a variance of less than 3%.

It was considered that the most relevant descriptors for drug aerosolization were the percentage delivered dose (total dose emitted from the DPI as a percentage of the loaded dose) and the FPF (stage 2

of the TSI, $< 6.4\,\mu m$) of the loaded dose (FPF_{LD}). It is important to note, however, that the FPF commonly is determined as the dose collected from stage 2 as a percentage of the delivered dose and not of the loaded dose. However, in cases where large deviations in delivered dose occur (i.e., where the delivered dose becomes very small), this standard method of determination may lead to exaggerated FPF values.

All in vitro experiments were performed in triplicate at 15, 30, 45, 60, and 75% RH at 25°C.

RESULTS AND DISCUSSION

Physical Characterization

In order to understand the effect of humidity on the three micronized materials, it is important that the particles are characterized in terms of particle size and morphology.

Median $d_{0.5}$ particle diameters for DCSG, salbutamol sulphate, and TAA were calculated as 5.44 μm, 4.79 μm and 4.39 μm, respectively, by using refractive indices of 1.3, 1.32, and 1.29, respectively. This suggests all three micronized drugs were of similar size and were suitable for inhalation applications. True density measurements for DSCG, salbutamol sulphate, and TAA were determined as $1.604\,g\,cm^{-3}$, $1.309\,g\,cm^{-3}$ and $1.318\,g\,cm^{-3}$, respectively.

Low-temperature scanning electron micrographs for the micronized DSCG, salbutamol sulphate, and TAA samples from the original batches are shown in Fig. 1a, b, and c, respectively. Representative photomicrographs of the "as supplied" DSCG and salbutamol sulphate (Fig. 1A, B) suggest that the crystals have a prismatic, columnar crystal shape, with the salbutamol sulphate sulphate shape appearing to be more homogeneous. Photomicrographs of the "as supplied" TAA (Fig. 1C) suggest the crystal form to have an irregular plate-like crystal shape. The LTSEM studies of the micronized drugs after exposure to 75% RH for 12 hr (not shown here) revealed no recognizable change in crystal shape or relative size. The formation of solid–liquid bridges between individual powder particulates also was not observed after storage at 75% RH, suggesting capillary interactions as the most likely source of cohesion at higher humidity.

X-ray powder diffraction patterns of DSCG, salbutamol sulphate, and TAA are presented in Fig. 2a, b, and c, respectively. The staggered

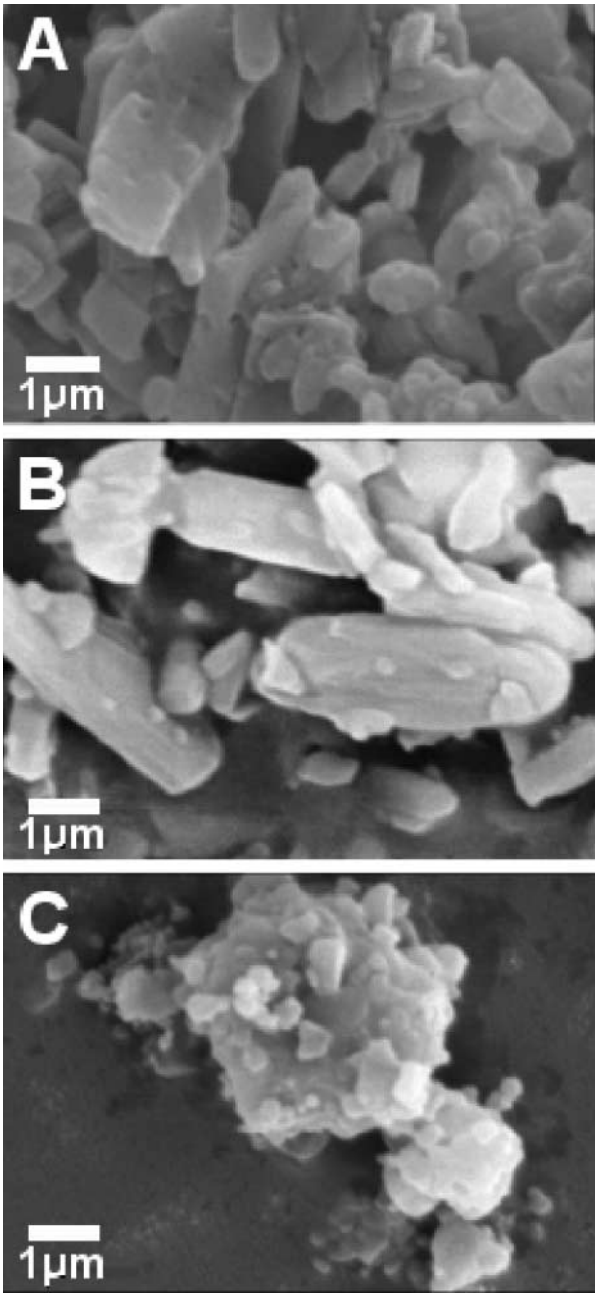

Figure 1. Low-temperature scanning electron micrographs (magnification ×15,000) of (A) DSCG, (B) salbutamol sulphate, and (C) TAA.

diffraction patterns for DSCG taken at 15, 30, and 75% RH (Fig. 2A), exhibited subtle differences in the relative peak intensities, most likely relating to sorption of water into the crystal lattice.[15–17]

Disodium cromoglycate is a nematic, chormonic liquid crystal that, below 93% RH, forms a solid solution.[15–17] The crystal structure can be classed

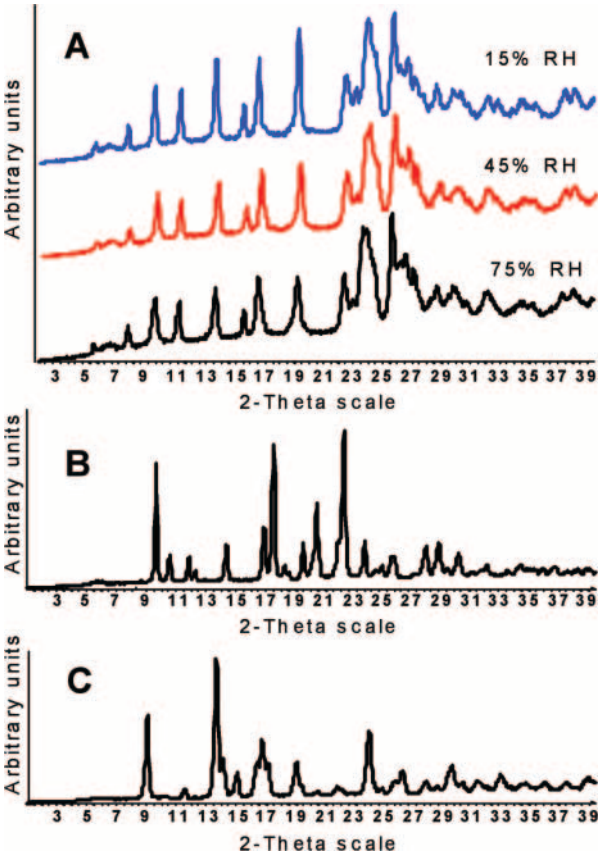

Figure 2. X-ray powder diffraction patterns of (A) DSCG staggered at 15, 45, and 75% RH; (B) salbutamol sulphate overlaid at 15, 45, and 75% RH; and (C) TAA overlaid at 15, 45, and 75% RH.

as an interstisial solid of "stacked" cromoglycate groups (rods) held together by water molecules.[15–17] Adsorption of water into the crystal structure is totally reversible and is accompanied by modification of the cromoglycate molecule torsional angles. Consequently, this will have a direct influence on the crystal structure and, therefore, x-ray powder diffraction pattern (XRPD). Diffraction patterns for DSCG correlated well with reports made previously.[17]

The XRPD patterns for salbutamol sulphate and TAA (Fig. 2B and C, respectively) exhibited no change in diffraction patterns at 15, 45, and 75% RH, suggesting that the presence of water vapor has no effect on the crystal lattice.

Karl Fischer–obtained moisture equilibrium profiles for DSCG, salbutamol sulphate, and TAA, as a function of humidity, are presented in Fig. 3 and are calculated as percentage water in the total mass.

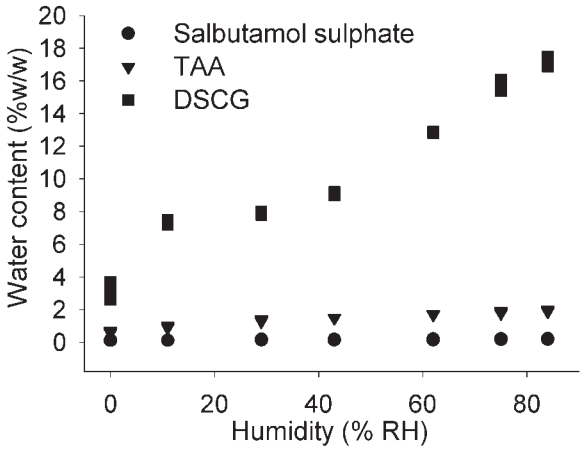

Figure 3. Percentage equilibrium moisture content of the micronized drugs after storage at different relative humidities (%w/w) at 25°C for salbutamol sulphate, TAA, and DSCG.

Analysis of the Karl Fischer water contents suggested a significant (ANOVA $p < 0.05$), positive increase in water content, for all three micronized drugs, as the storage humidity was increased. The water content of salbutamol sulphate was the least effected by storage humidity, increasing from $0.11 \pm 0.01\%$ w/w at 0% RH to $0.19 \pm 0.03\%$ w/w water content after storage at 84% RH. The TAA water content increased from $0.63 \pm 0.06\%$ w/w at 0% RH to $1.97 \pm 0.03\%$ w/w after storage at 84% RH. In comparison, the DSCG water content increased from 3.17 ± 0.55 at 0% RH to $17.17 \pm 0.31\%$ w/w on storage at 84% RH.

The large moisture sorption for DSCG is indicative of the drug's crystal nature. As previously stated, DSCG is effectively an interstitial solid solution, consisting of cromoglycate molecules staked in rods, held together by water molecules. Subsequently, considerable moisture sorption into the crystal lattice can occur. In general, the moisture sorption profile for DSCG correlated well with previous investigations.[15]

Moisture sorption of salbutamol sulphate and TAA was indicative of mono/multilayer water sorption onto the crystal surface. Karl Fischer values for salbutamol sulphate correlated well with previously reported values[18,19] by using dynamic vapor sorption. Larger sorption values for TAA, however, could not be fully explained. Since TAA is an insoluble steroid material with a well-defined x-ray powder diffractogram (indicating crystal structure), the relatively large moisture uptake ($1.97 \pm 0.03\%$ w/w at 84% RH) may be due to a larger surface

Table 1. Effect of varying humidity on the aerosolization performance of micronized DSCG, salbutamol sulphate, and TAA at 25°C.

Drug	Humidity (±2% RH)	% loaded dose in DPI	% loaded dose in TSI throat	% loaded dose in TSI stage 1	% loaded dose in TSI stage 2 (FPF_{LD})
DSCG	15	16.3 (0.4)	34.8 (6.0)	18.9 (7.1)	29.2 (9.0)
	30	36.2 (11.1)	17.0 (9.6)	21.8 (18.4)	23.0 (5.7)
	45	39.7 (11.5)	19.9 (12.9)	20.0 (6.5)	17.3 (7.4)
	60	74.4 (39.1)	4.2 (3.9)	16.6 (14.3)	1.2 (1.0)
	75	92.1 (10.2)	1.1 (1.8)	2.1 (1.8)	0.1 (0.0)
Salbutamol sulphate	15	14.8 (5.5)	10.7 (3.2)	62.0 (10.3)	12.5 (3.4)
	30	17.9 (3.6)	10.4 (1.1)	57.3 (6.8)	14.4 (2.7)
	45	26.9 (3.5)	11.8 (1.5)	47.9 (9.3)	13.3 (1.5)
	60	37.4 (8.5)	7.5 (1.3)	44.0 (10.0)	10.8 (2.8)
	75	87.4 (10.9)	2.0 (2.5)	7.9 (9.9)	2.7 (3.7)
TAA	15	31.5 (3.3)	30.2 (3.2)	32.3 (1.1)	6.0 (1.9)
	30	23.2 (5.0)	34.2 (7.1)	34.6 (4.9)	7.9 (0.6)
	45	21.5 (5.6)	25.1(1.0)	45.1 (3.7)	8.3 (0.9)
	60	25.8 (4.7)	22.7 (4.0)	42.0 (7.6)	9.5 (3.5)
	75	21.8 (6.2)	23.9 (6.8)	41.9 (14.9)	12.3 (3.5)

area (due to plate-like morphology) or possibly chemisorption of water.

In Vitro Characterization

The in vitro characterization of the aerosolization of DSCG, salbutamol sulphate, and TAA was conducted at 15, 30, 45, 60, and 75% RH at 25°C by using a TSI. The results obtained from the in vitro investigations are shown in Table 1 and are represented as percentage remaining in device, percentage in TSI throat and mouthpiece adaptor, percentage in stage 1, and percentage in stage 2.[13] Large standard deviations in the stage recoveries of the TSI can be attributed to a nonoptimized formulation containing "as supplied" micronized drug particles only. The aerosolization (FPF_{LD}) of all three micronized drugs was significantly affected by variations in humidity (ANOVA, $p < 0.05$), and can be seen graphically in Fig. 4.

Increased humidity had the greatest impact on the aerosolization efficiency of DSCG, with the mean percentage delivered dose falling from 82% at 15% RH to 3% at 75% RH. The data in Table 1 suggest that there is a significant decrease (ANOVA, $p < 0.05$) in both the delivered dose and the stage 2 recoveries at higher humidity levels. In order to compare the significance of this observation, a Fisher pair-wise analysis ($p < 0.05$) was performed for stage 2 recoveries at paired humidities. No

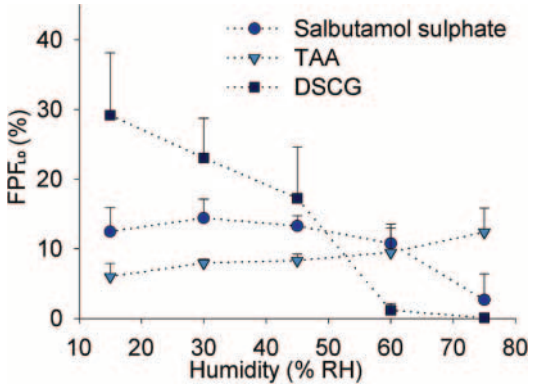

Figure 4. Effect of humidity on the percent FPF_{LD} (< 6.4 μm) for salbutamol sulphate, DSCG, and TAA ($n = 3$).

significant differences were observed at paired humidities 15–30, 30–45, and 60–75% RH, however, a significant difference between 45–60% RH and all remaining unpaired combinations was observed, suggesting a change over the whole humidity range, with the greatest impact on DSCG fine-particle aerosolization (< 6.4 μm) acting between the humidities 45% and 60% RH.

A plot of FPF_{LD} against humidity, presented in Fig. 4, suggests a decrease in mean FPF_{LD} of DSCG, between 15% and 45% RH, which may be attributed to the relative uptake (1.6% w/w) in water across the

same range (Fig. 3). It also is important to note that the FPF_{LD} of DSCG across the range 15% to 45% RH was greater than that of both salbutamol sulphate and TAA in all cases. This may be due to a higher density ($1.604\,g\,cm^{-3}$) and particle size ($5.44\,\mu m$) of DSCG, as the forces acting in a turbulent airstream to break up agglomerates will be directly related to particle mass.

An increase in humidity from 45 to 60% RH resulted in a large statistically significant decrease in DSCG FPF_{LD} to such an extent that only 1.2% (± 1.0) of the loaded dose was deposited in stage 2 of the TSI. Again, this large decrease in aerosolization performance could possibly be attributed to a large increase (3.7% w/w) in moisture uptake at 60% RH. An increase in the humidity from 60 to 75% RH resulted in a further increase (3% w/w) in DSCG moisture sorption, of similar magnitude as for the transition from 45% to 60% RH; this was coupled with a decrease in deposition to all stages of the TSI, with 92.1% (± 10.2) of the loaded dose remaining in the DPI, effectively terminating powder aerosolization.

The relationship between increased humidity and decreased aerosolization performance of DSCG most likely is attributed to the hygroscopic nature of the powder, because water is rapidly absorbed into the crystal lattice at a specific humidity until it forms an equilibrium with the surrounding environment.[15] The presence of such a dynamic equilibrium can only promote the condensation of water between the capillaries of the powder particulates, thus increasing the interparticulate forces while decreasing the aerosolization efficiency.

A significant decrease in the aerosolization efficiency of salbutamol sulphate at higher humidities also was observed (ANOVA, $p < 0.05$), however, the Fisher pair-wise analysis ($p < 0.05$) of both the delivered and the stage 2 deposition showed this to be significant between 60% and 75% RH only. Moisture sorption profiles (Fig. 3), of the salbutamol sulphate showed little increase in water across the range 15% to 75% RH, with a total water content of 0.2% w/w, at 75% RH in comparison with 15.8% w/w (± 0.4) moisture for the DSCG over the same range. These observations suggest that water is being appreciably adsorbed onto the crystal surface of salbutamol sulphate, making the rapid condensation of water between capillaries only likely when the humidity approaches saturation.[5]

In contrast to DSCG and salbutamol sulphate, the FPF_{LD} of TAA (Fig. 4) exhibited a small but statistically significant (ANOVA, $p < 0.05$) increase in FPF_{LD} across the humidity range 15% to 75% RH. Statistical analysis of the mean percentage delivered dose showed no significant difference across the humidity range, therefore, suggesting that the variation in aerosolization efficiency was related to particle-particle interactions. The improved aerosolization efficiency of TAA at higher humidities may be attributed to the dissipation of triboelectrification-induced surface charges. Such charges may be a consequence of the irregular plate-like structure of TAA (Fig. 1C), facilitating increased particle-particle contact area. A 1% w/w increase in moisture content of TAA between 11% and 75% RH would almost certainly allow the mobilization of electrons on the particulate surfaces, leading to possible charge dissipation. Such observations indicate electrostatic forces to be a dominating factor between micronized TAA particulates.

CONCLUSIONS

This investigation has shown three micronized drug materials to have significantly different aerosolization profiles when exposed to and aerosolized in different humidities. The relationship between humidity and aerosolization of micronized material can be attributed to the balance of interparticulate forces acting between the individual particulates, the proportion of each being related to the physical and chemical properties of the material.

However, it is important to note that such an investigation is a theoretical case study, in which the micronized drugs are used "as supplied" and, therefore, are nonoptimized formulations. This, none the less, provides invaluable information that can be applied when developing a formulation program for such drugs.

Consequently, the direct formulation of a micronized material is not a straightforward one, highlighting the importance for an individual formulation approach.

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