Protective Effect of Sodium Stearate on the Moisture-induced deterioration of Hygroscopic Spray-dried Powders

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Abstract

Amorphous powders are thermodynamically unstable, significantly impacting the processing, storage and performance of a product. Therefore, stabilization of the amorphous contents is in demand. In this study, disodium cromoglycate (DSCG) powder was chosen as a model drug because it is amorphous and highly hygroscopic after spray drying. Sodium stearate (NaSt) was co-spray dried with DSCG at various concentrations (10, 50 and 90% w/w) to investigate its effect against moisture-induced deterioration on the *in vitro* aerosolization performance of DSCG. Particle size distribution and morphology were measured by laser diffraction and scanning electron microscopy (SEM). Physicochemical properties of the powders were analysed by X-ray powder diffraction (XRPD) and dynamic vapour sorption (DVS). Particle surface chemistry was analysed by the time-of-flight secondary ion mass spectrometry (ToF-SIMS). *In vitro* dissolution behaviours of the SD powders were tested by the Franz cell apparatus. *In vitro* aerosolization performance of SD formulations stored at different relative humidity (RH) was evaluated by a multi-stage liquid impinger (MSLI), using an Osmohaler® at 100 L/min. Results showed that adding NaSt in the formulation not only increased the aerosolization performance of DSCG significantly, but also effectively reduced the deleterious impact of moisture. No significant difference was found in the fine particle fraction (FPF) of formulations containing NaSt before and after storage at both 60% and 75% RH for one week. However, after one month storage at 75% RH, SD formulation containing 10% NaSt showed a reduction in FPF, while formulations containing 50% or 90% NaSt showed no change. The underlying mechanism was that NaSt increased the crystallinity of the powders and its presence on the particle surface reduced particle aggregations and cohesiveness. However, NaSt at high concentration could reduce dissolution rate, which needs to be taken into consideration.

Keywords: Dry powder inhaler (DPI); Moisture protection; Aerosol performance; Spray drying; Excipients

1. Introduction

Amorphous or partially amorphous pharmaceuticals are of interest for drug delivery to the lungs (Weers and Miller 2015, Chen, Okuda et al. 2016). The amorphous content in the pharmaceutical powders can be unwantedly produced or intentionally designed (Burnett, Thielmann et al. 2004, Yu, Chan et al. 2017). Regardless, amorphousness plays an important role in solid pharmaceutical systems, directly affecting the powder processing, storage and delivery (Burnett, Thielmann et al. 2004). In particular, stability related issues during powder processing and storage are a major concern as even a small amount of amorphous material could absorb relatively large amounts of moisture, significantly impacting the long-term stability and performances.

Spray drying is one primarily used technique for inhalable dry powder production, while often leaving the powders amorphous and physically unstable (Vehring 2008). Subsequently, particle agglomerates may occur when the amorphous content absorbed moisture upon exposure to humidity (Zhou, Loh et al. 2016), causing adverse effects on the aerosol generation and lung deposition. One potential strategy for the prevention of moisture-induced deterioration in aerosolization performance is by coating moisture protective materials on the particle surface (Raula, Thielmann et al. 2008). Zhou et al. reported that SD colistin powders showed 30% decrease in FPF after storage at 75% RH for 24 h. However, no deterioration in FPF at the same storage condition was observed by co-spray drying with azithromycin at 1:1 mass ratio (Zhou, Loh et al. 2016). The protection was attributed to the occupying of azithromycin (96.5% molar fraction) on the co-SD particle surface (Zhou, Loh et al. 2016). Li et al. found that compared with SD DSCG powder, co-SD formulations containing 10-20% w/w L-leucine could achieve 61-73% (molar percent) coverage on the particle surface, and reduced the moisture-induced deterioration of DSCG after storage at 75% RH for 24 h but not after 4 weeks (Li, Sun et al. 2016). In our recent study, three hydrophobic amino acids, isoleucine, valine and

methionine, significantly reduced the deleterious effect of moisture on aerosol performance of DSCG, and the mechanism of the moisture protection was also related to the coverage of the amino acids on the particle surface (Yu, Chan et al. 2017).

Excipients were widely used in inhaled dry powder formulations in literature, but only a few have been approved by the FDA, including lactose monohydrate, 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), Calcium chloride ($CaCl_2$), gelatin, sulfuric acid, magnesium stearate (MgSt), titanium dioxide (TiO_2) and mannitol ((FDA) 2017). MgSt is a well-known excipient which can be obtained from animals and vegetables, and it has been widely used as a lubricant in solid dosage form (Shur, Price et al. 2016). Low moisture sorption behaviour was observed for MgSt under the RH exposure up to 90% (Swaminathan and Kildsig 2001). Previous studies by Zhou et al. showed that 2% w/w MgSt had a substantial improvement in the aerosolization behaviour the micronized salbutamol sulphate powder after mechanofusion (Zhou, Qu et al. 2013). MgSt was reported to protect the drug from moisture and to reduce cohesion and adhesion between particles (Young, Cocconi et al. 2002, Lau, Young et al. 2017). MgSt, however, is almost completely insoluble in water or most organic solvent system, often being used via mechanical approaches (Kumon, Machida et al. 2008, Zhou, Qu et al. 2010, Zhou, Denman et al. 2011, Zhou, Qu et al. 2011, Zhou, Qu et al. 2013). Compared with MgSt, NaSt is more soluble in water or co-solvent system (supplementary materials), being more potential to be used as a surface coating material via spray drying (Parlati, Colombo et al. 2009). Thus, NaSt was chosen as an excipient in this study to investigate its effect on the moisture protection of hygroscopic SD DSCG powders.

2. Materials and methods

2.1 Materials

DSCG was purchased from Zhejiang Esun Chemical Co., Ltd. (Hangzhou, China) and sodium stearate was sourced from ACROS Organics (New Jersey, USA). Phosphate buffered saline (PBS) and L-ascorbic acid were purchased from Sigma-Aldrich (Castle Hill, Australia). All the chemicals were of analytical grade except the HPLC grade methanol. Deionized water was from Modulab Type II Deionization System (Sydney, Australia). High purity compressed nitrogen gas (North Ryde, Australia) was used for spray drying. Commercial Osmohaler® inhaler was sourced from Pharmaxis Ltd. (Frenches Forest, Australia) and hydroxypropyl methylcellulose transparent size 3 capsules were from Capsugel (West Ryde, Australia).

2.2 Powder formulation

A feed solution (10 mg/ml total solutes) was prepared by dissolving NaSt and DSCG at a known mass ratio (10%, 50% and 90% mass ratio) in 50% ethanol using a 40 °C water bath. The drug solution was pumped into a B-290 lab scale spray-dryer (Büchi Falwil, Switzerland) connected to a B-295 inert loop (Büchi Falwil, Switzerland). High purity dry nitrogen was used as the atomizing gas. The spray-dryer was operated at the following conditions: feed rate of 1.8 mL/min, atomizer setting 742 L/h, aspirator of 35 m^3/h, inlet N_2 temperature 100 °C and outlet N_2 temperature 68-70 °C. After spray drying, all powders were stored in a desiccator containing silica gel at room temperature for further analysis.

2.3 Particle size

A Scirocco 2000 accessory dry powder dispersion unit (Malvern Instruments, UK) was applied for particle size distribution measurement of the SD powders, under an air pressure of 2.0 bar. D_{10}, D_{50}, and D_{90} (i.e. particle size under 10%, 50% and 90%, respectively) and span (i.e. difference between D_{10} and D_{90} divided by D_{50}) were calculated from the size distribution results. Each formulation was measured in triplicate.

2.4 Particle morphology

Powders from each formulation was spread on a stub and sputter coated with 15 nm thick gold using a Quorum Emitech K550X sputter coater (Kent, UK). A Carl Zeiss scanning electron microscopy (Oberkochen, Germany) at 3 kV was used for capturing SEM images of the particle morphology.

2.5 Crystallinity

Crystallinity of the powder was measured on a Shimadzu X-ray powder diffraction (XRPD) 6000 (Kyoto, Japan) with Cu-Kα radiation set at 40 kV and the current at 30 mA. The results were recorded from 5º to 50° by the 2θ method at a scan speed of 2° per minute.

2.6 Dynamic water vapour sorption

A dynamic vapour sorption system (DVS-1, Surface Management Systems, London, UK) was used for measuring the moisture sorption behaviour of the SD samples. 5-10 mg of powder was placed in the measurement chamber under a continuous N_2 gas flow at 25 °C. The RH inside the chamber was maintained in the range of 0-90%, with 10% increments or decrements for the sorption and desorption cycle, respectively. Moisture uptake was considered to have reached equilibration when the value of weight change dm/dt was smaller than 0.002 % per minute.

2.7 Time-of-Flight secondary ion mass spectrometry

Time-of-Flight secondary ion mass spectrometry was conducted on a Physical Electronic TRIFT V nanoToF instrument (Physical Electronics Inc., Chanhassen, MN, USA) which was equipped with a pulsed liquid metal $^{79+}$Au primary ion gun (LMIG) under 30 keV energy operate in either “bunched” mode to optimize mass resolution and “unbunched” mode to optimize spatial resolution for imaging. Dual charge neutralization was provided by a 10 eV electron flood gun and 10 eV Ar+ ions. All experiments were carried out under a vacuum of 5×10^{-6}Pa or lower. All data was collected and interpreted with WinCadenceN software

130 (ULVAC-PHI Inc., Chanhassen, MN, USA). More detailed descriptions could be found in
131 published works elsewhere (Zhou, Denman et al. 2011, Zhou, Qu et al. 2011, Zhou,
132 Gengenbach et al. 2014, Li, Sun et al. 2016, Wang, Zhou et al. 2016).

133 Pure DSCG and NaSt were analysed to identify their responses before the components were
134 mapped in the co-SD formulations. The obtained data were then compared qualitatively by
135 preparing plots of average normalized counts with 95% confidence intervals for each fragment
136 of interest (Li, Sun et al. 2016). In this study, the mass spectra collected for DSCG and NaSt
137 were analysed by the following dominants, characteristic responses: m/z ~181 ($C_3H_3O_2^+$) and
138 ~229 atomic mass unit (amu) for DSCG, and m/z ~127 ($C_3H_5^+$) amu for NaSt.

139 **2.8 Powder storage**

140 Powders were stored separately in an open clean glass vial for each formulation in a humidity
141 cabinet (Thermoline, Australia) at 60% RH or in a desiccator containing saturated sodium
142 chloride solution (75% RH), both at 25 °C for one week and one month.

143 **2.9 *In vitro* aerosolization performance**

144 A multi-stage liquid impinger (Copley, UK) connected to a USP throat with a silicone
145 mouthpiece adapter (Westech Instrument, UK) was employed to analyse the *in vitro* aerosol
146 performance of the SD powers before and after storage. 4 L of air was passed through the
147 Osmohaler® (Pharmaxis Ltd., Australia) at a flowrate of 100 L/min for 2.4 seconds, at 4 kPa
148 pressure drop across the device. The cut-off diameters of stages 1-4 at such flow rate are 10.4,
149 4.9, 2.4 and 1.2 μm, respectively. 10 ± 1 mg of powders were loaded in a size 3 capsule
150 (Capsugel, Australia) and then dispersed through the Osmohaler® device in a controlled
151 environment cabinet at 25 ± 2 °C and the targeted RH. Particles deposited on the capsule,
152 inhaler, adapter, throat and stages would be rinsed carefully with deionized water and then
153 collected for chemical assay. The glass filter was washed and sample was centrifuged at 13,400

rpm for 20 minutes (Westbury, USA) to obtain the supernatant. Dispersion for each formulation was carried out in triplicate.

2.10 *In vitro* dissolution profile of DSCG

A Franz cell dissolution system together with a heated stirring station (V6B, Perm Gear Inc., Bethlehem, U.S.A.) were applied to test the *in vitro* dissolution profiles of the four SD formulations. PBS (pH=7.4) containing 2% ascorbic acid was used as dissolution medium and the liquid temperature was maintained at 37 °C throughout the experiment by a water bath. Further details of the method were described elsewhere (Chan, Chan et al. 2013, Parumasivam, Chan et al. 2016, Wang, Zhou et al. 2016).

Powder samples (2.0 to 3.0 mg) deposited on a 0.45 μm cellulose filter paper were weighed accurately and the filter paper was then placed in between the buffer meniscus of the Franz cell. At predetermined time points within 3 hours, approx. 550 μl of aliquot was withdrawn from the dissolution medium and replaced with the same amount of fresh buffer. After measurement, the filter membrane was removed and washed with 3 mL of fresh buffer solution. DSCG drug was quantified using a HPLC method described below. Each formulation was measured in triplicate.

2. 11 Drug quantification

A high-performance liquid chromatography system (Shimadzu, Japan) and a Luna C18 column (μm, 250 × 4.60 mm; Phenomenex, USA) were applied to determine the concentration of DSCG (Li, Sun et al. 2016). The mobile phase consisted of 0.025 mol/L monobasic potassium phosphate (pH=3.0) and methanol at 55:45 (v/v) ratio. UV detection wavelength was 326 nm, flow rate was 1.0 ml/min and injection volume was 20 μl. Fresh standards were prepared prior to each HPLC measurement.

Emitted dose fraction (ED, %) was defined as the total mass percentage of the drug particles collected from all parts except the capsule and inhaler device relative to the total recovered drug. Fine particle fraction (FPF, %) was defined as the total mass percentage of the drug particles with an aerodynamic diameter smaller than 4.9 μm (i.e., the total amount of drug particles collected from stage 2 and below) relative to the total recovered drug.

2. 12 Statistical analysis

One-way analysis of variance (ANOVA) software was applied for testing statistical differences. The statistically differences were considered as significant if the probability values were less than 0.05.

3. Results

3.1 Physicochemical properties

3.1.1 Particle size

Table 1 presented the particle size distribution results of the SD powder formulations. Most particles of each formulation had relatively narrow size distribution of less than 5 μm and with spans in the range of 1.0-2.0, which were suitable for DPI formulation. Among all SD formulations, DSCG alone had a relative small D_{50} value of 1.07 ± 0.02 μm, and D_{50} values of co-SD formulations containing NaSt were around 1.5 μm.

3.1.2 Particle morphology

Results of particle size observed by SEM observation (Fig. 1 and 2) and measured by laser diffraction were in good agreement. Figure 1 (a, b and c) showed the morphology of SD DSCG powder particles stored under different conditions. Similar to our previous study (Yu, Chan et al. 2017), the morphology of SD DSCG particles (Fig. 1a) was near-spherical with rough surfaces. After storage at 60% (Fig. 1b) and 75% RH (Fig. 1c) for one week, the particles fused

into solid aggregates. Figure 2(A-C)-1 showed the powder morphology of co-SD formulations containing NaSt. Overall, increasing the amount of NaSt resulted in particles with corrugated surfaces. After storage at 60% and 75% RH for one week, the surface morphology of particles in these formulations remained unchanged, being unaffected by the moisture. While after being stored at 75% RH for one month, the SD DSCG particles (Fig. 3a) became irregular and collapsed, which were similar to our previous study (Yu, Chan et al. 2017). In contrast, particle morphology of the co-SD formulations containing NaSt was maintained (Fig. 3b-d).

3.1.3 Crystallinity

A broad peak was shown at 25º in the XRPD diffractogram (Fig. 4a) of SD DSCG powders, suggesting the amorphous state. In contrast, SD NaSt showed distinct peaks (e.g. at 7º, 12°, 20º and 24º), confirming the crystalline form. For co-SD formulations containing NaSt, the intensities of peaks were related to the ratio of two components. Overall, increasing the amount of NaSt resulted in more distinguishable crystalline peaks compared with SD DSCG particles. After one month storage at 75% RH, the XRPD diffractogram of the SD powders (Fig. 4b) changed, with the occurrence of small crystalline peaks at different angles (10°, 25º and 28º). The XRPD patterns of formulations containing 50% and 90% NaSt were less affected compared with the formulation containing 10% NaSt, which may be related to their aerosol performances against moisture (in later discussion).

3.1.4 Water sorption

SD pure DSCG powders underwent a significant mass increase (up to 50%) at the dynamic water sorption cycle ranging from 0-90% RH (Fig. 5a), which was similar to our previous study (Yu, Chan et al. 2017). In contrast, SD pure NaSt absorbed about 3% at the elevated RH. With increasing amount of NaSt in the formulations, moisture uptake at the elevated RH was decreased. Interestingly, the water uptake and the percentage of DSCG showed a linear

relationship at certain RHs (Fig. 5b), suggesting that in the co-SD formulations, NaSt had little effect on the water uptake by DSCG. For the co-SD powders, all formulations exhibited a similar reversible moisture sorption trend with no moisture induced recrystallization. All tested formulations showed a desorption hysteresis behaviour as the water molecules escaped slower during desorption cycle (Zhu, Tan et al. 2008).

3.1.5 Distribution of NaSt on the particle surface

As the peaks correlating to the larger ion fragments were of low intensity, characteristic smaller mass fragments with higher intensity were used to visualize the distribution of NaSt and DSCG on the surface of the samples. Figure 6 (a-e) shows the overlay of the chemical distribution of $C_3H_5^+$ (green) and $C_3H_3O_2^+$ (red) from NaSt and DSCG, respectively, as imaged via ToF-SIMS. ToF-SIMS probes the chemical composition at an average depth of 1-2 nm. The overlay images of $C_3H_5^+$ and $C_3H_3O_2^+$ demonstrate the change of surface composition towards complete NaSt surface coverage with increasing concentration ratio in the formulation.

The relative amount of DSCG and NaSt on the particle surface is difficult to quantify due to the similarity in elemental composition between the two compounds. However, it was observed that the normalized intensity of DSCG specific mass fragment (at m/z ~229 amu) peaks showed a decreasing trend with the increase of NaSt in the formulation (Fig. 7). The presence of this fragment in the 10% NaSt sample revealed an incomplete surface overage by the NaSt. As the concentration of NaSt is increased to 50% and 90%, DSCG associated peaks decrease to levels comparable to the NaSt control. This suggests that the outermost surface of these formulations entirely consists of NaSt.

3.2 *In vitro* aerosolization performance

Figure 8 (a-d, desiccator) showed the aerosolization performance of SD powders. All spray-dried formulations had a high emitted dose of > 85%. There was no significant difference in

248 the emitted dose ($p > 0.05$) among formulations. The FPF and ED for SD DSCG alone were
249 68.1 ± 4.8% and 85.4 ± 5.8%, respectively. The dispersion results showed that co-SD
250 formulations had a significantly higher FPF ($p < 0.05$) compared with SD DSCG alone, via a
251 reduction of particle retention in the capsule and significant deposition increases in the
252 impactor stage 4 and filter stage ($p < 0.05$). For co-SD powders containing 10% w/w NaSt, the
253 ED and FPF were increased to 88.5 ± 0.6% and 85.5 ± 1.0%, respectively. Interestingly,
254 formulations with higher amount of NaSt (50% and 90%) did not show further improvement
255 in the aerosol performance of the DSCG.

256 **3.3 Effect of humidity on aerosolization**

257 Figure 8 also presented the aerosol performance of SD formulations after one week and one
258 month of storage at 60% and 75% RH, respectively. The FPF of SD DSCG alone powder fell
259 dramatically to 39.6 ± 3.3% at 60% RH and 6.3 ± 1.17% at 75% RH, respectively (Fig. 8a). In
260 contrast, the presence of NaSt significantly reduced the effects of moisture on the aerosol
261 performance of DSCG. There is no significant difference in the FPF ($p > 0.05$) of co-SD
262 powders containing 10%, 50% and 90% NaSt before and after storage at both 60% and 75%
263 RH for one week. However, after storage at 75% RH for one month, SD '10% NaSt+90%
264 DSCG' showed a significant decrease in FPF (74.7 ± 3.3 %, $p < 0.05$). In contrast, formulations
265 containing 50% or 90% NaSt maintained the FPF ($p > 0.05$) of the DSCG (84.3 ± 2.0% and
266 86.8 ± 1.7%, respectively) under the same storage condition. Interestingly, SD '10% NaSt+90%
267 DSCG' could maintain the FPF (85.8 ± 0.8%) after being stored at 60% RH for one month (in
268 supplementary materials).

269 **3.4 *In vitro* dissolution profiles of DSCG**

270 Figure 9 showed the *in vitro* dissolution results of DSCG from the Franz cell measurement. SD
271 DSCG and SD 10% NaSt+90% DSCG had similar rapid dissolution profiles, where about 60%

of total drug dissolved in the first 15 min. Formulations containing 50% and 90% NaSt had a slower dissolution rate, with approximately 40 and 20% of drug dissolved in the first 15 min, respectively. The maximum drug dissolved in 3 hours for SD DSCG and SD 10% NaSt+90% DSCG powders was about 90%, which was reduced by approx. 15% and 25% in formulations containing 50% and 90% NaSt, respectively.

4. Discussion

The hygroscopic nature of the SD powders is a challenge since moisture uptake can result in both physical and chemical instabilities of solid dosage forms (Li, Sun et al. 2016). DSCG powders after spray drying were amorphous and underwent a significant mass increase of 50% from water absorption at 90% RH. After storage at 75% RH for one week, the FPF of SD DSCG particles fell dramatically and became not inhalable. In the current study, we found that NaSt had a positive effect on improving the aerosolization performance as well as protecting DSCG against moisture. Results showed that formulation containing 10% NaSt preserved the FPF at elevated RH (60% and 75%) storage conditions for one week, but failed at 75% RH storage for one month. However, when the content of NaSt was increased to 50% and 90%, the co-SD formulations maintained the FPF even after storage at 75% RH for one month. In addition, formulations containing 50% and 90% NaSt showed a slower *in vitro* dissolution rate of DSCG, due to coating of the particles by NaSt which is less water soluble than DSCG (see below). Although the '10% NaSt' formulation showed a 45% mass increase at 90% RH, the existence of NaSt in the formulation showed a significant difference in protection against moisture-induced deterioration compared with SD DSCG powder alone. The moisture protective mechanism was probably attributed to the enrichment of NaSt on the particle surface, reducing particle-particle and particle-moisture interactions, thus facilitating dispersions. When two or more components were dried together in a droplet, redistribution on the particle surface can be driven by the difference in diffusivity, solubility, density, surface activity and

297 hydrophobicity of each component (Porowska, Dosta et al. 2016). In this study, the molecular
298 weight of DSCG and NaSt is 512.3 and 306.5 g/mol, respectively, suggesting that they would
299 have similar diffusion rate when dried in a droplet and thus could be evenly distributed
300 throughout the drying solid. However, NaSt has a much lower aqueous solubility than DSCG
301 (Index 1968) and is a surface active (Tay, Morton et al. 2012). Therefore, this hydrophobic
302 excipient would accumulate at the droplet liquid-gas interface during drying and deposits on
303 the dried particles surface (Parlati, Colombo et al. 2009), as seen in the Tof-SIMS images (Fig.
304 6). The early formulation of an NaSt-enriched shell could have prevented further shrinkage of
305 the particles, resulting in slightly larger particle size for the co-SD formulations (Table 1). The
306 accumulated NaSt on the surface would result in a large reduction in interfacial tension between
307 the contiguous microparticles (Parlati, Colombo et al. 2009), leading to a significant
308 improvement of the aerosolization efficiency as well as moisture protection for the dry powder
309 formulations. Another factor that contributed to the moisture protection is likely the
310 crystallinity of NaSt, as materials in the crystalline state will typically have less water vapor
311 sorption than the amorphous state due to the reduction in free energy, void space and/or surface
312 area (Burnett, Thielmann et al. 2004). As shown in the XRPD (Fig. 4a), formulations
313 containing 50% or 90% NaSt showed higher intensities of crystalline peaks compared with
314 formulation containing 10% NaSt. More interestingly, we found that after one month storage
315 at 75% RH, there were less changes in the XRPD patterns of powders containing 50% and 90%
316 NaSt compared with those containing 10% NaSt (Fig. 4b), which was also consistent with the
317 aerosolization performances against moisture. During the drying process, NaSt was expected
318 to reach supersaturation early in the process and crystallized out (Sadd, Lamb et al. 1992). The
319 presence of non-hygroscopic crystalline NaSt on the particle surface reduced the potential of
320 interactions between particle surface and moisture (Li, Sun et al. 2016), thereby reducing the
321 water uptake (Fig. 5a). However, after being stored at 75% RH for one month, SD '10% NaSt

+ 90% DSCG' showed a significant decrease in FPF, which is likely due to the incomplete surface coverage of NaSt. We have also investigated formulations containing 0.1% and 1.0% NaSt and found their aerosol performances deteriorated dramatically after one week storage at 75% RH similar to the SD DSCG powder (supplementary materials), further supporting the moisture protection offered by NaSt is concentration dependent.

5. Conclusions

The addition of NaSt in inhalable powder formulations not only improved the *in vitro* aerosol performance, but also decreased moisture-induced deterioration in aerosolization. The proposed mechanism for this enhancement is the crystallinity and coverage of NaSt on the particle surface. This in turn is dependent on the concentration of NaSt present in the formulation. This investigation broadens the current understanding on sodium stearate as a moisture protective excipient on hygroscopic powders for inhalation drug delivery.

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Table Captions

Table 1. Particle size distribution of SD powder formulations measured by laser diffraction. Mean ± SD, n = 3

Legend to figures

Figure 1. SEM micrographs of SD DSCG alone powder at different conditions: (a) Desiccator; (b) 60% RH one week; (c) 75% RH one week.

Figure 2. SEM micrographs of SD powder formulations containing NaSt and DSCG at different ratios: (A) SD 10% NaSt+90% DSCG; (B) SD 50% NaSt+50% DSCG; (C) SD 90% NaSt+10% DSCG; 1-Desiccator; 2-60% RH one week; 3-75% RH one week.

Figure 3. SEM micrographs of SD powder formulations containing NaSt and DSCG at different ratios under 75% RH for one month: (a) SD DSCG; (b) SD 10% NaSt+90% DSCG; (c) SD 50% NaSt+50% DSCG; (d) SD 90% NaSt+10% DSCG

Figure 4. X-ray powder diffraction patterns of SD powder formulations, (a) desiccator (b) 75% RH, one month.

Figure 5. (a) Dynamic water sorption behaviour of SD powder formulations; (b) relationships between the percent of DSCG in the formulations and water uptake at different RHs.

Figure 6. Overlay mapping of $C_3H_5^+$ (green) and $C_3H_3O_2^+$ (red) on the surface of particles measured by ToF-SIMS (scale bar represents 10 μm): (a) NaSt; (b) DSCG; (c) SD 10% NaSt+90% DSCG; (d) SD 50% NaSt+50% DSCG; (e) SD 90% NaSt+10% DSCG.

Figure 7. Graph of normalized intensity of the DSCG specific mass fragment at m/z ~229 amu.

Figure 8. The effect of moisture on *in vitro* aerosolization performances of SD NaSt/DSCG powders: (a) SD DSCG, (b) SD 10% NaSt+90% DSCG, (c) SD 50% NaSt+50% DSCG, and (d) SD 90% NaSt+10% DSCG.

Figure 9. Dissolution profiles of DSCG from SD formulations.