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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 spray-dried (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.

1. Introduction

Amorphous or partially amorphous pharmaceuticals are of interest for drug delivery to the lungs (Weers and Miller, 2015; Chen et al., 2016). The amorphous content in the pharmaceutical powders can be unwantedly produced or intentionally designed (Burnett et al., 2004; Yu et al., 2017). Regardless, amorphousness plays an important role in solid pharmaceutical systems, directly affecting the powder processing, storage and delivery (Burnett 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 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 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 et al., 2016). The protection was attributed to the occupying of azithromycin (96.5% molar fraction) on the co-SD particle surface (Zhou 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 et al., 2016). In our recent

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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 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 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 et al., 2013). MgSt was reported to protect the drug from moisture and to reduce cohesion and adhesion between particles (Young et al., 2002; Lau et al., 2017). MgSt, however, is almost completely insoluble in water or most organic solvent system, often being used via mechanical approaches (Kumon et al., 2008; Zhou et al., 2010, 2011a,b, 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 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 were 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 5° 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 were collected and interpreted with WinCadenceN software (ULVAC-PHI Inc., Chanhassen, MN, USA). More detailed descriptions could be found in published works elsewhere (Zhou et al., 2011a,b, 2014; Li et al., 2016; Wang et al., 2016).

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

2.8. Powder storage

Powders were stored separately in an open clean glass vial for each formulation in a humidity cabinet (Thermoline, Australia) at 60% RH or in a desiccator containing saturated sodium chloride solution (75 ± 5% RH), both at 25 °C for one week and one month.

2.9. In vitro aerosolization performance

A multi-stage liquid impinger (Copley, UK) connected to a USP throat with a silicone mouthpiece adapter (Westech Instrument, UK) was employed to analyse the *in vitro* aerosol performance of the SD powers before and after storage. 4 L of air was passed through the Osmohaler® (Pharmaxis Ltd., Australia) at a flowrate of 100 L/min for