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Research paper

Protection of hydrophobic amino acids against moisture-induced deterioration in the aerosolization performance of highly hygroscopic spray-dried powders

Jiaqi Yu [a], Hak-Kim Chan [a,*], Thomas Gengenbach [b], John A. Denman [c]

[a] Advanced Drug Delivery Group, Faculty of Pharmacy, The University of Sydney, New South Wales 2006, Australia
[b] CSIRO Manufacturing, Bayview Avenue, Clayton, Victoria 3168, Australia
[c] Future Industries Institute, University of South Australia, Mawson Lakes, South Australia 5095, Australia

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Disodium cromoglycate (PubChem CID: 27503)
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ABSTRACT

Background: Inhalable particles containing amorphous form of drugs or excipients may absorb atmospheric moisture, causing powder aggregation and recrystallization, adversely affecting powder dispersion and lung deposition. The present study aims to explore hydrophobic amino acids for protection against moisture in spray-dried amorphous powders, using disodium cromoglycate (DSCG) as a model drug.

Materials and methods: DSCG powders were produced by co-spray drying with isoleucine (Ile), valine (Val) and methionine (Met) in various concentrations (10, 20 and 40% w/w). Particle size distribution and morphology were measured by laser diffraction and scanning electron microscopy (SEM). Physiochemical properties of the powders were characterized by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and dynamic vapor sorption (DVS). Particle surface chemistry was analyzed by X-ray photoelectron spectroscopy (XPS) and time-of-flight secondary ion mass spectrometry (ToF-SIMS). *In vitro* aerosolization performance was evaluated by a next generation impactor (NGI) after the powders were stored at 60% or 75% relative humidity (RH) for one month and three months.

Results and discussion: Ile, Val and Met significantly reduced the deleterious effect of moisture on aerosol performance, depending on the amount of amino acids in the formulation. Formulations containing 10% or 20% of Ile, Val and Met showed notable deterioration in aerosol performance, with fine particle fraction (FPF) reduced by 6–15% after one-month storage at both 60% and 75% RH. However, 40% Ile was able to maintain the aerosol performance of DSCG stored at 75% RH for one month, while the FPF dropped by 7.5% after three months of storage. In contrast, 40% Val or Met were able to maintain the aerosol performance at 60% RH storage but not at 75% RH. At 40% w/w ratio, these formulations had particle surface coverage of 94.5% (molar percent) of Ile, 87.1% of Val and 84.6% of Met, respectively, which may explain their moisture protection effects.

Conclusion: Ile, Val and Met showed promising moisture protection effect on aerosol performance. The results broaden the understanding on the use of hydrophobic amino acids as an excipient for long-term storage of inhalation powders formulations that are hygroscopic.

1. Introduction

Pharmaceutics that are amorphous or partially amorphous gained increasing interests for inhalation drug delivery [1,2]. Amorphous materials can be unwantedly produced, or deliberately designed (e.g. for increased dissolution rate) during powder processing [3]. Regardless, the existence of amorphous materials in pharmaceutical powders can affect the processing, storage and delivery properties of the powder [4]. If stored improperly, amorphous powders would absorb relatively large amounts of water from surroundings, and impact significantly the long-term stability and performance.

Dry powder for inhalation drug delivery produced by spray drying are often amorphous and physically unstable [5–7]. While most studies of dry powder inhalers (DPI) have focused on the

* Corresponding author.
E-mail address: kim.chan@sydney.edu.au (H.-K. Chan).

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aerosolization performance of the powder formulation, stability issues related to moisture-related stability and deterioration of aerodynamic behavior have received less attention. Moisture uptake can adversely impact powder aerosol generation and subsequently lung deposition. Adi et al. reported that spray-dried (SD) ciprofloxacin powders were amorphous and could absorb 7.9% w/w water when exposed to 50% RH. Recrystallization occurred at 70% RH and co-SD formulations containing ciprofloxacin and 50% w/w mannitol prevented recrystallization [8]. The authors explained this could result from the existence of mannitol throughout the matrix and/or a decrease amount of bound water in the SD sample [8]. Zhou et al. found that the storage of SD hygroscopic colistin powders at 75% RH after 24 h could lead to a significant FPF reduction (approx. 30%), while co-SD colistin containing hydrophobic azithromycin at 1:1 mass ratio did not deteriorate in FPF at the same storage condition [9]. The protection was attributed to azithromycin occupying the surface of the co-SD particles, with 96.5% molar fraction on the particle surface at 1:1 mass ratio [9]. Very recently, Li et al. also reported co-SD formulations containing 10–20% (w/w) L-leucine (L-Leu) reduced the moisture-induced deterioration of DSCG after stored at 75% RH for 24 h but not after 4 weeks [10]. It is probable that the incomplete shielding of L-Leu (with 61–73% molar ratio) on the particle surface would have left voids for water to absorb into the particles [10]. Besides Leu, there are other naturally occurring amino acids which are hydrophobic and could potentially be used as excipients against moisture. Amino acids are regarded as endogenous materials with relative less safety considerations for pulmonary drug delivery [1].

In the present study, hydrophobic amino acids isoleucine (Ile), valine (Val) and methionine (Met) were evaluated for their moisture-protection effects on SD amorphous powders of DSCG as a model hygroscopic drug.

2. Materials and methods

2.1. Materials

Disodium cromoglycate raw material was purchased from Zhejiang Esun Chemical Co., Ltd. (Hangzhou, Zhejiang, China). L-isoleucine, L-valine and DL-methionine were all purchased from Sigma-Aldrich (Castle Hill, New South Wales, Australia). All the chemicals were analytical grade except the HPLC grade methanol. Deionized water was obtained from Modulab Type II Deionization System (Continental Water System, Sydney, Australia). Commercial Osmohaler® inhaler was from Pharmaxis Ltd. (Frenches Forest, Australia) and hydroxypropyl methylcellulose transparent size 3 capsules were from Capsugel (Capsugel, West Ryde, Australia).

2.2. Powder formulations

A spray drying feed solution (10 mg/mL total solutes) containing one of the three amino acids and DSCG at mass ratios of 1:9, 2:8, and 4:6 was prepared by dissolving the two drugs in the deionized water. The drug solution was pumped into the spray dryer (B-290 mini spray-dryer, Büchi Falwil, Switzerland) at a feed rate of 1.8 mL/min. The spray dryer was operated under the following conditions: inlet air temperature 80 °C and outlet air temperature 53–54 °C, atomizer setting 742 L/h, aspirator of 35 m^3/h. After spray drying, all the powders were stored in a desiccator containing silica gel at room temperature for further experiments.

2.3. Particle size

Particle size distribution of the SD formulations were measured by laser diffraction with a Scirocco 2000 accessory dry powder dispersion unit (Mastersizer 2000, Malvern Instruments Ltd., UK) with

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

	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)	Span
DSCG	0.73 ± 0.04	1.54 ± 0.03	2.99 ± 0.02	1.46 ± 0.06
1Ile + 9DSCG	0.76 ± 0.01	1.64 ± 0.01	3.22 ± 0.02	1.49 ± 0.01
2Ile + 8DSCG	0.72 ± 0.04	1.49 ± 0.02	2.85 ± 0.05	1.43 ± 0.08
4Ile + 6DSCG	0.72 ± 0.02	1.58 ± 0.01	3.11 ± 0.08	1.52 ± 0.06
Ile	1.12 ± 0.01	1.81 ± 0.03	2.91 ± 0.08	0.99 ± 0.05
1 Val + 9DSCG	0.75 ± 0.01	1.64 ± 0.01	3.22 ± 0.02	1.50 ± 0.01
2 Val + 8DSCG	0.75 ± 0.02	1.60 ± 0.01	3.12 ± 0.10	1.48 ± 0.07
4 Val + 6DSCG	0.71 ± 0.03	1.57 ± 0.02	3.10 ± 0.06	1.52 ± 0.07
Val	1.24 ± 0.14	2.24 ± 0.04	3.49 ± 0.20	0.99 ± 0.02
1Met + 9DSCG	0.83 ± 0.02	1.75 ± 0.03	3.36 ± 0.04	1.45 ± 0.02
2Met + 8DSCG	0.72 ± 0.01	1.60 ± 0.01	3.20 ± 0.02	1.54 ± 0.01
4Met + 6DSCG	0.74 ± 0.02	1.46 ± 0.03	2.73 ± 0.03	1.36 ± 0.01
Met	1.34 ± 0.01	2.21 ± 0.01	3.59 ± 0.01	1.01 ± 0.01

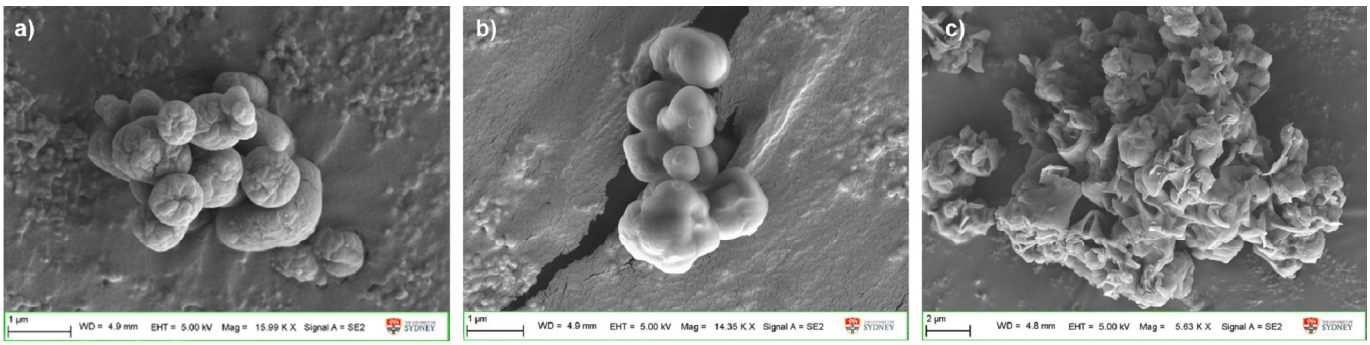

Fig. 1. SEM micrographs of spray-dried DSCG alone powder at different conditions: (a) Desiccator; (b) 60% RH one month; (c) 75% RH one month.