Effect of Amino Acids on the Dispersion of Disodium Cromoglycate Powders

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ABSTRACT: Modified disodium cromoglycate powders were prepared by co-spray drying with different concentrations of leucine, phenylalanine, tryptophan, methionine, asparagine, and arginine. Amorphous spherical particles of the same size and density where obtained which, however, exhibited different surface properties as measured by the inverse gas chromatography (IGC) and X-ray photoelectron spectroscopy (XPS) techniques. The surface energy parameters, such as the dispersive component of surface free energy of the sample, γ_S^D, and the total solubility parameter, δ, were significantly lower in the presence of nonpolar chain amino acids, particularly with leucine and phenylalanine, than pure DSCG. However no quantitative relationship between these parameters, the additive concentrations, and the fine particle fractions, FPF, determined for different inhalers and air flow rates, was observed. The FPF significantly increased with addition of leucine and this effect was attributed to reduced intermolecular interactions between leucine and disodium cromoglycate molecules, as indicated by the difference in corresponding Hansen solubility parameters. Decrease of interparticle interactions for leucine-containing powders also led to a lesser dependence of FPF on the flow rate and inhaler type. J Pharm Sci 94:2289–2300, 2005

Keywords: dry powder aerosols; emitted dose; fine particle fraction; surface energy; leucine

INTRODUCTION

Effective inhalation delivery requires the overcoming of particle aggregation, induced by electrostatic, van der Waals, and capillary interactions between particles. A number of approaches have been employed attempting to obtain good aerosol properties, including the use of fine and coarse carrier particles,[1,2] the modification of surface characteristics,[3,4] low density or porous particles,[5] and the inclusion of excipients.[6] Amino acids, in particularly leucine, is one class of excipient that has been found to improve powder aerosol properties.[7–10] For example, the work by Lechuga-Ballesteros and Kuo[11] has shown that a powder formulation containing a peptide, which has at least two leucyl residues, can provide a highly dispersible aerosol formulation. In this work, the enhancement of powder dispersion was attributed to the reduction of the

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interfacial tension of solution with addition of di- and tri-peptides, which were surface active. Because the particles were obtained using a spray-drying process, it was proposed that the overall specific surface energy of the solid phase correlated with the droplet surface tension.

The surface energy has been recognized to be a very important factor affecting both the cohesive and adhesive forces between particles.[12–14] Unfortunately, the direct measurement of this parameter is impossible. An accepted approach involves analysis of the dispersive component of the surface free energy, γ_S^D, and the specific components of surface free energies of adsorption, ΔG_A, obtained from inverse gas chromatography (IGC).[15,16] γ_S^D can be considered as the portion of the total surface energy constituted by the dispersive van der Waals forces. ΔG_A is the free energy of adsorption of a solvent probe on a solid surface, and therefore comprises polar interaction energies contributed by both the probe and the solid surface. More quantitative assessment of the overall surface energy can be done on the basis of Hildebrand solubility parameter, δ,[16,17] which consists of individual parts arising from (atomic) dispersion force, (molecular) permanent dipole-permanent dipole forces, and (molecular) hydrogen bonding. Although such an approach has been successfully used to explain the dispersion and aerosolization behavior of several crystalline drugs produced by jet-milling and supercritical fluid precipitation processes,[12,13,15–19] its validity in the general case can be questioned. For example, the recent work by Schiewe and Zierenberg[20] concerns particle interactions of several inhalable drugs, employing Handihaler® dry powder inhaler (DPI). It was concluded that combined analytical methods such as IGC and atomic force microscope (AFM) had no predictive power for ranking the micronized drugs according to their deagglomeration behavior with this DPI. Shekunov et al.[12] showed that powder dispersion is governed by multiple interrelated parameters such as powder and particle density, particle size and aggregate structure, particle shape factor, surface morphology, and aerodynamic flow regime which may produce a greater effect on particle dispersion than the surface energy. There is also a question of the IGC data interpretation for amorphous and composite drug-excipient materials or solid solutions which often show very good dispersion profiles despite their supposedly high surface energies when compared to more ordered crystalline structures. It has been suggested by Chow et al.[15] that a typical IGC analysis, based on infinite dilution of liquid probes, may not give an adequate or complete picture of the surface energy mapping. In addition, the contribution of the entropy to the magnitude of the surface free energy is significant and may only be taken into account using a series of measurement at different temperatures.[16] Thus it can be concluded that powder dispersion in DPI is a very complex phenomenon and, in order to understand which effects dominate, the particulate properties should be well-defined leaving only surface energy parameters as independent variables.

The effect of particle size on the aerosol performance of disodium cromoglycate was studied elsewhere.[21] In this work, spherical amorphous particles of the controlled size and density were produced by spray drying of disodium cromoglycate with various amino acids. The concentration of these additives was selected as the major control parameter. The surface energetics was determined by IGC and the powder aerosolization performance was judged by measuring FPF at different air flow rates and for two different inhalers.

MATERIALS AND METHODS

Preparation of DSCG and Amino Acids Containing Powders

DSCG raw material was a gift from Aventis, Sydney, Australia. Amino acids, leucine (LEU), phenylalanine (PHE), methionine (MET), tryptophan (TRP), arginine (ARG), asparagine (ASN), were obtained from Sigma (St. Louis, MO).

Spray dried DSCG and amino acid containing DSCG powders were prepared by a Büchi 191 Mini Spray Dryer (Flawil, Switzerland). The feed solution contained only DSCG or amino acid and DSCG at known wt.% ratio (see Tabs. 1 and 2) were dissolved in deionized water. The total concentration in solution was 10 mg/mL. The spray drying conditions were: inlet temperature 90°C, feed rate 1.4 mL/min, aspiration 57.3 m^3/h. The spray dried powders after collection were stored over phosphorous pentoxide until use.

Solid State Characterization

Particle sizing

Particle size distribution of the powders was measured in suspensions using a Mastersizer S Laser Diffractometer (Malvern, Worcs, UK) as described previously.[21] Chloroform was used as a