European Journal of Pharmaceutics and Biopharmaceutics xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research Paper

Relationship between surface concentration of L-leucine and bulk powder properties in spray dried formulations

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ARTICLE INFO

Article history:
Received 9 February 2015
Accepted in revised form 29 April 2015
Available online xxxx

Keywords:
L-Leucine
Polyvinylpyrrolidone
Surface mapping
Inter-particle cohesion
Spray drying

ABSTRACT

The amino acid L-leucine has been demonstrated to act as a lubricant and improve the dispersibility of otherwise cohesive fine particles. It was hypothesized that optimum surface L-leucine concentration is necessary to achieve optimal surface and bulk powder properties. Polyvinylpyrrolidone was spray dried with different concentration of L-leucine and the change in surface composition of the formulations was determined using X-ray photoelectron spectroscopy (XPS) and time of flight-secondary ion mass spectrometry (ToF-SIMS). The formulations were also subjected to powder X-ray diffraction analysis in order to understand the relationship between surface concentration and solid-state properties of L-leucine. In addition, the morphology, surface energy and bulk cohesion of spray dried formulations were also assessed to understand the relation between surface L-leucine concentration and surface and bulk properties. The surface concentration of L-leucine increased with higher feed concentrations and plateaued at about 10% L-leucine. Higher surface L-leucine concentration also resulted in the formation of larger L-leucine crystals and not much change in crystal size was noted above 10% L-leucine. A change in surface morphology from spherical to increasingly corrugated particles was also recorded. Specific collapsed/folded over particles were only seen in formulations with 10% or higher L-leucine feed concentration suggesting a change in particle surface formation process. In addition, bulk cohesion also reduced and approached a minimum with 10% L-leucine concentration. Thus, the surface concentration of L-leucine governs particle formation and optimum surface L-leucine concentration results in optimum surface and bulk powder properties.

1. Introduction

Fine particles (typically <10 μm) are routinely found in a range of dry powder pharmaceutical operations and continue to attract significant research interest [1,2]. Such fine powders have been explored in tablet formulations for their enhanced dissolution and tendency to form interactive mixtures particularly in the context of low-dose formulations to achieve content uniformity [2,3]. However, the major challenge with the use of such fine particles is their highly cohesive nature and a tendency to agglomerate which can limit their extent of use and effectiveness in dry powder applications [4,5]. In practice, particle cohesion needs to be controlled to limit agglomeration and also facilitate de-agglomeration.

Co-spraying materials with L-leucine have been shown to limit agglomeration and improve dispersion of fine particles mainly in the context of inhaled drug delivery [6,7]. It has been proposed that the use of L-leucine will reduce cohesion and improve dispersibility by controlling the surface texture of spray dried particles [8,9]. L-Leucine is believed to migrate to the surface of the droplets followed by formation of a shell early in the drying phase [10]. This L-leucine rich shell interferes with the diffusion of water vapour leading to formation of corrugated particles [11]. Corrugated particles experience significantly reduced contact area and consequently lower inter-particle cohesion [12,13].

A recent study proposed that rather than surface corrugation, the solid-state properties of L-leucine play a leading role in

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http://dx.doi.org/10.1016/j.ejpb.2015.04.035
0939-6411/

determining its effectiveness in controlling cohesion [14]. It was proposed that L-leucine crystallizes early in the spray drying owing to its low water solubility [11]. Crystals of L-leucine exhibit lower mobility in the receding/drying droplet and result in formation of an L-leucine enriched shell. It was also reported that the effectiveness of L-leucine increases as its crystallinity increases and the optimum effectiveness is typically achieved in the formulations with fully crystalline L-leucine [14]. However, L-leucine was recently also argued to exist as a partially ordered molecular structure, which was proposed to be result of its lamellar self-assembly on the surface of the spray dried particles [15].

Recently, our group illustrated that the enhanced powder properties achieved by co-spraying cohesive materials with L-leucine could be used to create a multi-functional interactive excipient for tablet formulations [16]. It was demonstrated that L-leucine achieves substantially higher concentrations on the surface than the bulk and results in significant reduction in surface energy of spray dried formulations [16]. However, it is unknown how L-leucine affects the surface energy and particle formation of the spray dried formulations. However, the influence of surface structure and concentration of L-leucine on physico-chemical and bulk powder properties is relatively unexplored. In this study, we hypothesized that the surface concentration L-leucine dictates surface physico-chemical properties which in turn determines the bulk properties. In addition, optimum surface physico-chemical and bulk powder properties are achieved at optimum surface L-leucine concentration. This insight could help understanding supporting a "quality by design" approach to optimize formulation performance.

For this study polyvinylpyrrolidone (PVP) was spray dried with different concentrations of L-leucine. The surface composition of spray dried formulations was examined using state-of-the-art techniques: X-ray photoelectron spectroscopy (XPS) and time of flight-secondary ion mass spectrometry (ToF-SIMS). The solid-state property of L-leucine was determined using powder-X-ray diffraction (P-XRD), while the surface physico-chemical properties such as surface energy and morphology were determined using inverse gas chromatography (IGC) and scanning electron microscopy (SEM) respectively. Finally, the intrinsic bulk cohesion of the powders was determined using powder shear testing.

2. Materials and methods

PVP (average molecular weight 10,000 Da), was purchased from Sigma–Aldrich (St. Louis, Missouri, USA). L-Leucine was purchased from Ajinomoto Co. Inc. (Tokyo, Japan). Acid washed silanized glass beads (250 μm) were obtained from Sigma (Sigma Aldrich, Steinheim, Germany).

2.1. Method of preparation

Aqueous solutions of PVP in combination with various proportions of L-leucine (as shown in Table 1) were spray dried using the method as described previously [17]. Briefly, PVP and leucine were weighed accurately and dissolved in water with the aid of magnetic stirring. The resultant solutions were spray dried using a Buchi-190 mini spray-dryer (Buchi Laboratory Equipment, Flawil, Switzerland) with a 0.5 mm two-fluid nozzle. The standard operating conditions employed during spray-drying were: inlet temperature, 125 ± 5 °C; spray air flow rate, 800 L/h and liquid solution feed rate, 10 mL/min. These conditions resulted in an outlet temperature of 70 ± 2 °C. The powders then obtained were collected immediately and stored in a sealed aluminium bag to prevent exposure to humidity.

Table 1
Compositions of various spray dried formulations.

Formulation codes	PVP (% w/v)	L-Leucine (% w/w of L-leucine)
PVP-Leu (0%)	6	0
PVP-Leu (2.5%)	6	2.5
PVP-Leu (5%)	6	5
PVP-Leu (7.5%)	6	7.5
PVP-Leu (10%)	6	10
PVP-Leu (12.5%)	6	12.5
PVP-Leu (15%)	6	15

2.2. Particle size and size distribution

The particle size and size distribution of the spray dried formulations were determined by laser-light scattering method using the Malvern Mastersizer 2000 (Malvern Instruments Ltd., Worcestershire, UK) equipped with a Sirocco cell dry powder dispersion unit. A shear pressure of 2.0 bar was used to disperse the powders in air to achieve efficient de-agglomeration. Obscuration was in the range of 2–5. The particle size values D_{50} (50% volume median diameter), D_{10} (10% volume below this diameter) and D_{90} (90% volume below this diameter), span and particle size distribution plots were collected and the average values of three measurements were reported.

2.3. Scanning electron microscopy (SEM)

The surface morphology of the various formulations was imaged by scanning electron microscopy (Phenom™, FEI Company, Hillsboro, Oregon, USA). A small amount of powder sample was scattered on the aluminium stub mounted with carbon tape and excess powder was removed using air gun. The stubs were then coated with a thin gold film using a sputter coater (Emitech K550X, Quorum Technologies, Kent, UK). The gold coated stubs were then loaded in the instrument and images were captured.

2.4. X-ray photoelectron spectroscopy (XPS)

X-ray photoelectron spectroscopy (XPS) analysis was performed using an AXIS Ultra DLD spectrometer (Kratos Analytical Inc., Manchester, UK) with a monochromated Al Kα source at a power of 180 W (15 kV × 12 mA), a hemispherical analyser operating in the fixed analyser transmission mode and the standard aperture (analysis area: 0.3 mm × 0.7 mm). The total pressure in the main vacuum chamber during analysis was typically 10^{-8} mbar. Survey spectra were acquired at a pass energy of 160 eV. To obtain more detailed information about chemical structure, oxidation states, etc., high resolution spectra were recorded from individual peaks at 20 eV pass energy (yielding a typical peak width for polymers of 1.0 eV). Samples were filled into shallow wells of custom-built sample holders. One lot of each sample was prepared and 2 different locations were analysed on each sample at a nominal photoelectron emission angle of 0° with respect to the surface normal. Since, the actual emission angle is ill-defined in the case of such fine particles (ranging from 0° to 90°) the sampling depth may range from 0 nm to approximately 5–10 nm. The atomic concentrations of the detected elements were calculated using integral peak intensities and the sensitivity factors supplied by the manufacturer. Binding energies were referenced to the aliphatic hydrocarbon peak at 285.0 eV.

2.5. Time-of-flight secondary ion mass spectrometry (ToF-SIMS)

ToF-SIMS experiments were performed using a Physical Electronics Inc. PHI TRIFT V nanoTOF instrument (Physical

Please cite this article in press as: S. Mangal et al., Relationship between surface concentration of L-leucine and bulk powder properties in spray dried formulations, Eur. J. Pharm. Biopharm. (2015), http://dx.doi.org/10.1016/j.ejpb.2015.04.035