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Investigations on particle surface characteristics vs. dispersion behaviour of L-leucine coated carrier-free inhalable powders

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ABSTRACT

Aerosol microparticles of salbutamol sulphate are gas-phase coated with an amino acid L-leucine. Depending of the saturated state of L-leucine, the coating is formed by the surface diffusion of L-leucine molecules within a droplet or by the physical vapour deposition (PVD) of L-leucine or by the combination thereof. The PVD coated particles showed excellent aerosolization characteristics in a carrier-free powder delivery from an inhaler. The aerosolization of the fine powders is compared with surface energy parameters analysed by inverse gas chromatography (IGC). The dispersion testing is conducted by a Inhalation Simulator using a fast inhalation profile with inhalation flow rate of 67 l min^{-1}. It is found that the powder emission is affected by the morphology, surface roughness (asperity size and density) of the particles and acidity of particle surface. The latter affects the dispersion and dose repeatability of fine powder in a case if L-leucine content is high enough. However, there is no direct correlation between dispersive surface energies and aerosolization performances of the powders. Crucial factors for the improved aerosolization rely weakly on surface acid–base properties but strongly on particle morphology and fine-scale surface roughness.

1. Introduction

Particle interactions in solid dosage forms are of importance since they control many bulk properties such as flowability, dispersibility and mixing (Zeng et al., 2001; Young et al., 2006; Lohrmann et al., 2007). In inhalation therapy, a deep lung deposition of fine drug particles relies strongly on a particle–particle detachment and overcoming the interacting forces mainly caused by van der Waals but also electrostatic and capillary interactions. The cohesion forces become stronger with the reduced particle size. As a consequence, the dosing of fine particles becomes inaccurate and may alter drastically without additives such as coarse carriers. Today's market for the carrier-free formulations relies on inhaler technology to disperse loosely agglomerated micronized powders in a high turbulent flow inside the inhaler, e.g. Turbuhaler (Wetterlin, 1988; Tang and Kenyon, 2000). However, this delivery way is applicable to materials that cannot be subjected to the micronization process. Exubera® (Bindra and Cefalu, 2002) represents a different type of carrier-free formulation where insulin particles are spray dried.

Aerosolization of fine powders depends on physical properties such as particle size and size distribution, density, surface features such as molecular groups, nature and morphology. Particle surfaces have been modified, for instance, by excipients for better aerosolization (Zeng et al., 1998; Staniforth and Morton, 2002; Lucas et al., 1998). Amino acids, particularly leucine analogs, tend to improve the separation of the particles (Staniforth, 1996; Staniforth, 1997; Lucas et al., 1999; Ganderton et al., 2000; Lechuga-Ballesteros and Kuo, 2001; Chew et al., 2005; Raula et al., 2007a,b, 2008a). For instance, Begat et al. (2005) blended and mechanically fused force control agents including L-leucine with carriers and micronized drug powders to form thin coating layers. We recently demonstrated a novel simultaneous gas-phase coating method where the particles from nanometers to micrometers and of different materials were coated by the PVD of L-leucine (Raula et al., 2008a,b,c).

A curved surface with small asperities and low surface energy generally reduces the contact area between adjacent surfaces (Israelachvili, 1991; Podczeck, 1999; Li et al., 2006; Katainen et al., 2006). Particle shape and surface roughness reduce contact area and increase particle distance of separation. Lowered surface

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energy has been recognized to decrease cohesive and adhesive forces between particles. The highest surface energy of a material is encountered with extremely flat, smooth and clean surfaces. When this surface is contaminated with gas, liquid or solid particles the adhesion forces between the particles in contact may decrease drastically. This is a consequence of lowered surface energy and increased separation distance.

Since the direct measurement of surface energy is difficult to realize, and thus it is accepted to measure a dispersive component of the surface free energy (γ_S^D) and specific components of surface free energies of adsorption (ΔG_A^{SP}) using inverse gas chromatography (IGC) (Thielmann et al., 2007; Buckton and Gill, 2007; Batko and Voelkel, 2007; Davies et al., 2005; Ticehurst et al., 1994). IGC is particularly sensitive if measurements are carried out in the low concentration or infinite dilution regime (the linear or Henry portion of the isotherm). At infinite dilution conditions, very few probe molecules are available for an interaction with the surface of the material under investigation and will therefore only interact with the highest energy sites on the surface. For this reason even the smallest differences between similar materials or batches of the same material that have been processed under slightly different conditions can be measured by varying probe concentration, temperature, flow rate, or background relative humidity. γ_S^D is considered to describe the total surface energy constituted by the dispersive van der Waals forces and ΔG_A^{SP} is the free energy of adsorption of a solvent probe on a solid surface. When estimating surface energy of the solids, a common problem is that the energy is not distributed evenly over the entire surface area. Some topographically discontinuous regions such as edges and surface asperities may have higher surface energies than flat surfaces. Even different types of crystalline orders may have different surface energy. The surfaces of pharmaceutical powders are not 'polished' and possess always surface defects to give roughness of some level.

Consequently, the correlation of surface energy with other properties of a powder is not straightforward. IGC has been used in combination with other techniques to achieve better understanding of, for instance, the changes in material crystallinity when micronized (Feeley et al., 1998) or how powder preparation influence on powder properties (Rehman et al., 2004) or how environmental exposure such as humidity affect surface energetic (Sunkersett et al., 2001). There are many approaches to use ICG in explaining the aerosolization behaviour of the crystalline powders produced by jet-milling (Sethuraman and Hickey, 2002) (a type of micronization) and using supercritical fluid technology (Sunkersett et al., 2001). Chew et al. (2005) determined surface energetics of the DSCG powders co-spray dried with amino acids and attempted to correlate them with the aerosolization results of these powders. They found no strong correlation between fine particle fraction (FPF) and surface composition or surface energy parameters. However, the powders with a surface-diffused L-leucine performed higher FPF and the second lowest γ_S^D than the powders with other amino acids. The decreased interaction between these powders was hypothesized to be a result of irregular particle surface morphology formed upon the phase separation of L-leucine in the particle surface.

We have used an aerosol flow reactor method (Eerikäinen et al., 2003; Raula et al., 2004; Lähde et al., 2006) to prepare a set of L-leucine coated salbutamol sulphate micron-sized powders at different saturation conditions of L-leucine. The formation of the L-leucine coatings on different sized core particles composed of different material has been discussed in-depth elsewhere (Lähde et al., 2008a,b,c; Raula et al., 2007a, 2008d). The aerosolization behaviour of the carrier-free formulations was studied using an apparatus called Inhalation Simulator (Kauppinen et al., 2002; Kurkela et al., 2002) under fast inhalation mode. The aerosolization behaviours of some powders reviewed in this work have been studied earlier (Raula et al., 2008c). This study focuses to explore whether the surface energetics correlate with aerosolization performance of these powders and look for a true origin for improved dispersion.

2. Materials and methods

2.1. Preparation of the L-leucine coated powders

2.1.1. Materials

Salbutamol sulphate (Alfa Aesar, Germany) and L-leucine (Fluka, Switzerland) were used as received. For fine particle preparation, materials were co-dissolved in deionized water (pH 6; Millipore) to give precursor solutions where the concentration of salbutamol sulphate was 30 g/l and that of L-leucine were 2.5, 7.5 and 15 g/l.

2.1.2. Experimental

Principles of the method for the gas-phase coated solid salbutamol sulphate particles with L-leucine have been discussed in detail in our previous work (Raula et al., 2008b). Particle preparation in the aerosol flow reactor consists of the generation of droplets, drying of particles, and coating of dry solid particles via the PVD of L-leucine. Solute droplets from the precursor solutions were formed using an ultrasonic nebulizer (RBI Pyrosol 7901, France) and transferred with nitrogen gas ($(10.0 \pm 0.1)\,l\,min^{-1}$, 22 °C) to the reactor consisting of five stainless steel tubes (ID 3 cm, length 120 cm). Reactor temperatures were 100 and 160 °C (±1 °C). At the reactor downstream the aerosol was rapidly cooled with N_2 gas (22 °C) at $80\,l\,min^{-1}$ in a porous stainless steel tube (ID 3 cm, length 20 cm). The aerosol flow became turbulent with a Reynolds number over 3000. The cooling rate from 100–160 °C to 30 °C was 0.9–1.8 °C/ms. The particles were collected by a small-scale cyclone (Zhu and Lee, 1999) with a nominal cut-off diameter (D50) of 0.7 μm at the $90\,l\,min^{-1}$ as used in this work.

2.2. Dispersion experiments

2.2.1. Carrier-free powders

Aerosolization experiments were conducted with the carrier-free formulations meaning that all the fine powders whose flowability was sufficient for the delivery via the inhaler (Easyhaler®) were tested. The PVD coated fine powders and commercial micronized salbutamol sulphate powder, S_{micr} (a gift from Gamprex, Italy) were used for the testing. The powders were stored over silica (0–1% of relative humidity) prior to the inhalation experiments.

2.2.2. Inhalation simulator

The apparatus to study the aerosolization behaviour of powders is a computer-assisted Inhalation Simulator developed in-house (not commercial). Its detailed operating principles have been discussed elsewhere (Kauppinen et al., 2002). Briefly, the inhalation profile is created through interplay between vacuum and pressurized air gas by a controlled valve system. The inhaler, Easyhaler®, is loaded with a powder (in this work fine powder as such without coarser carrier particles) and then connected to a mouthpiece holder of the Inhalation Simulator. The inhaled air flows via the inhaler, takes the powder and transfers it to the device tubing. The powder emission is detected on-line by a light attenuation between two opposing IR probes lined at the exit of the inhaler and also gravimetrically. Inhalation run was performed 10 times and in between the runs the inhaler was knocked 3 times vertically as an upright position on the table prior to the dose loading and inhalation. The knocking procedure removed possible traces such as voids of the previous powder loading.

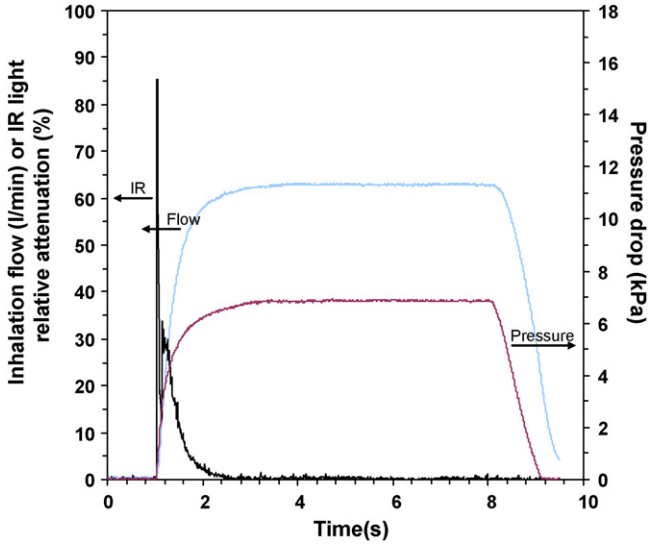

Fig. 1. Fast inhalation profile employed in the dispersion experiments of the carrier-free powder formulations. IR, infrared light attenuation; flow, inhalation flow rate; pressure, pressure drop over the inhaler.

2.2.3. Inhalation profile

Aerosolization experiments were carried out upon the fast inhalation profile (Fig. 1) where the flow rate of inhaled air increased abruptly from 0 l min^{-1} up to 67 l min^{-1} (±1 l min^{-1}) in 2 s. Then the maximum flow rate was maintained for 9 s. The initial acceleration of the flow was 132.3 l min^{-1} s^{-1} and initial accelerating pressure 17.2 kPa s^{-1}. Pressure over the inhaler at the maximum flow rate was 6.5–7.5 kPa. After the steady-state inhalation the flow decelerated with 53.2 l min^{-1} s^{-1} and 5.8 kPa s^{-1}.

2.3. Characterization

2.3.1. Powder characteristics

The number size distributions of the produced particles were determined with an electrical low-pressure impactor (ELPI; Dekati Ltd., Finland) wherefrom geometric number mean diameter (GNMD) and geometric standard deviation (GSD) were determined (Raula et al., 2008b). Oiled porous collection substrates (Dekati Ltd., Finland) with stage aerodynamic cut-off diameters from 0.03 to 7.88 μm were used to avoid particle bounce.

The morphologies of the particles were imaged with a field-emission scanning electron microscope (FE-SEM; Leo DSM982 Gemini, LEO Electron Microscopy Inc., Germany). The samples were sputter-coated with platinum in order to stabilize the particle under the electron beam and to enhance image contrast.

The compositions of precursor solutions and powders were determined by a nuclear magnetic resonance (NMR) spectrometer. Proton NMR measurements were conducted with a 200 MHz Varian Gemini 2000 spectrometer using deuterated water as the solvent. The characteristic chemical shifts used for salbutamol sulphate were 6.8–7.4 ppm (3H, phenyl protons) and for L-leucine 0.8–1.0 ppm (6H, methyl protons).

The volumes of the powder samples were measured in five or 25 consecutive determinations with a Micromeritics AccuPyc 1330 Pycnometer using helium as the measuring gas. The masses of the samples were determined before and after the measurement, and the averages were used to calculate the true densities.

2.3.2. IGC measurements

IGC measurements were carried out using the SMS-iGC 2000 and the SMS-iGC v1.3 standard analysis suite as well as SMS-iGC v1.21 advanced analysis suite of macros. A flame ionization detector (FID) was used to determine the retention times. The samples were prepared by packing powders into a silanized glass column (300 mm long and 3 mm inner diameter for all samples). All columns were analysed twice in a row to check for irreversible sorption effects and equilibrium after preconditioning. Two columns were analysed to check for heterogeneity within each sample. Each packed column was exposed to the following pre-treatment and measurement conditions. Initially, the column was pre-treated for 3 h at 30 °C and 0% RH to remove any species physisorbed on the surface. Then, the surface energy measurements were performed at 0% RH, 30 °C, 10 sccm total flow rate, 0.25 ml pulse injections and 0.93 p/po injection vapour concentration for all elutants. Measurements were performed with hexane, heptane, octane, nonane and decane as probes for the determination of the dispersive contribution of the surface energy. Specific free energies, representing the interaction between polar probes and the solid surface were determined using ethyl acetate, ethanol, acetone and acetonitrile.

2.3.3. Powder dispersion

The dispersed fine particles were collected isokinetically at the downstream of Inhalation Simulator by a Berner-type low-pressure impactor, BLPI, with a stage aerodynamic cut-off diameters ranging from 0.03 to 15.61 μm (Hillamo and Kauppinen, 1991). The particles were collected on the greased aluminum foils to avoid particle bouncing. The determination of a mass median aerodynamic diameter (MMAD) and related GSD have been determined by

$$\mathrm{MMAD} = \exp\left(\frac{\sum(m_i \ln D_i)}{M}\right) \quad (1)$$

$$\mathrm{GSD} = \exp\left(\left(\frac{\sum(m_i D_i^3(\ln D_i - \ln \mathrm{MMAD})^2}{\sum(m_i D_i^3) - 1}\right)^{1/2}\right) \quad (2)$$

respectively, where m_i is the mass fraction of particles on the collection stage and M is the sum of mass fractions and is, by definition, unity. Fine particle fraction (FPF, $D \leq 5$ μm) was expressed with reference to the emitted dose (ED) that was determined by the change in the mass of the inhaler after each inhalation run.

3. Results and discussion

3.1. Powder characteristics

3.1.1. Particle formation

L-Leucine possesses two features that can be utilized when preparing coated particles. These features are related to the saturation of L-leucine. First, in the condensed phase L-leucine enriches at the interface of air–water due to its surface activity in aqueous solution. Second, L-leucine sublimes forming vapour that can be in the later stage deposit on the surface of drug particles via heterogeneous nucleation. The formation of L-leucine coatings at different saturation conditions is studied in detail elsewhere (Lähde et al., 2008a,b,c; Raula et al., 2007a, 2008d).

The coating layer of L-leucine was solely formed by the surface diffusion when the reactor temperature was 100 °C. L-Leucine content in the powders was 50–56% to that in the precursor solutions (see Table 1).

It was observed in our earlier study (Raula et al., 2008b) that the sublimation of L-leucine initiated from the surface of salbutamol particles approx. 15–20 °C lower temperatures as it was estimated by vapour pressure calculations. At a certain temperature range a fraction of L-leucine sublimed while the rest remained on particle surface in a condensed state. Thus, the particles produced from the reactor at 160 °C contained two L-leucine coatings formed by surface diffusion (inner layer) and by physical vapour deposition

Table 1
Experimental conditions for the production of fine powders from the precursor solutions and powder characteristics. Abbreviations: S, salbutamol sulphate; L, L-leucine; C_{total}, total precursor solution concentration; T_R, reactor temperature.

Sample	Experimental conditions			Precursor solution			Produced powder		
	T_R (°C)	Sat. ratio[a]	Coating[b]	C_{total} (g/l)	S (w-%)[c]	L (w-%)[c]	S (w-%)[c]	L (w-%)[c]	True density[d] (g/cm^3)
S100-100	100	n.a.	n.a.	30.0	100	0	100	0	1.322
S96L04-100	100	>1 (2.7E+03)	i	32.5	92	8	96	4	1.270
S89L11-100	100	>1 (8.0E+03)	i	37.5	80	20	89	11	1.258
S97L03-160	160	>1 (4.3)	i + ii	32.5	92	8	97	3	1.271
S91L09-160	160	>1 (13.0)	i + ii	37.5	80	20	91	9	1.260
S82L18-160	160	>1 (17.3)	i + ii	45.0	67	33	82	18	1.237

[a] Calculated according to Raula et al., 2007a. Values in the brackets are momentary saturation ratios in supersaturated conditions.
[b] Particles coated (i) by surface diffusion and (ii) by PVD of L-leucine.
[c] ^{1}H-NMR in D_2O.
[d] Average of 5–25 measuring repetitions.

(outer layer). L-Leucine content in the powders ranged from 25% to 56% with the increasing content of L-leucine in the precursor solutions (see Table 1). The size (GNMD) varied between 1.6 and 1.8 μm and their width of distribution (GSD) between 1.6 and 1.9.

3.1.2. Morphology and nature of particle surface

As discussed above, the formation of the L-leucine coating was dependent on the saturation conditions of L-leucine. Fig. 2 shows the morphology of the uncoated and L-leucine coated salbutamol sulphate powders. The uncoated particles, S100-100, were spheres and smooth. When coated purely by the surface diffusion, the particle surfaces were smooth though their morphology became increasingly wrinkled as L-leucine content increased. The wrinkled structure has been previously interpreted as an indication of hollow particles. Indeed, particle density decreased along 'wrinkleness' of the samples (see Table 1). The true density of the micronized powder used in this work was 1.314 g/cm^3. Upon the vapour deposition, L-leucine crystallized forming asperities with size ranging from a few to several hundreds of nanometers on the core particle surfaces. Roughness, in terms of asperity size and density, became visually more distinctive as a content of L-leucine in the vapour phase prior to the deposition increased. The powders S91L09-160 and S82L18-160 that were wrinkled and having crystalline 'chips' on the surface proved the existence of the two L-leucine coating layers formed in conditions where L-leucine had been partially sublimed. Regardless on the coating manner, L-leucine showed a strong enrichment (>90% surface coverage) at the particle surfaces (Raula et al., 2008d).

3.2. Powder aerosolization and surface energetics

3.2.1. Aerosolization measurements

Dose uniformity of a drug is an essential parameter in drug delivery systems. Due to the cohesive nature of fine powders (diameter ≤10 μm) they are commonly blended with coarser carrier particles to ensure dose uniformity. However, the carriers, if made of lactose, may cause undesired side-effects to patients and thus, so-called carrier-free powder formulations are preferred. A prerequisite requirement for these types of formulations is good flowability and dispersibility.

Several studies show that the increased L-leucine content improves notably the dispersion of fine powders as delivered using the carrier blends (Lechuga-Ballesteros and Kuo, 2001; Chew et al., 2005; Raula et al., 2007b). The L-leucine coating formed by the surface diffusion results in cohesive system and fine particles could not be delivered without carriers (Raula et al., 2007b). Instead, the fine powders coated with the PVD of L-leucine performed good flowability and thus, could be delivered without the carriers. A reference fine powder, micronized salbutamol sulphate powder (S_{micr}), did not flow well but was flowable enough to be fed without the carriers.

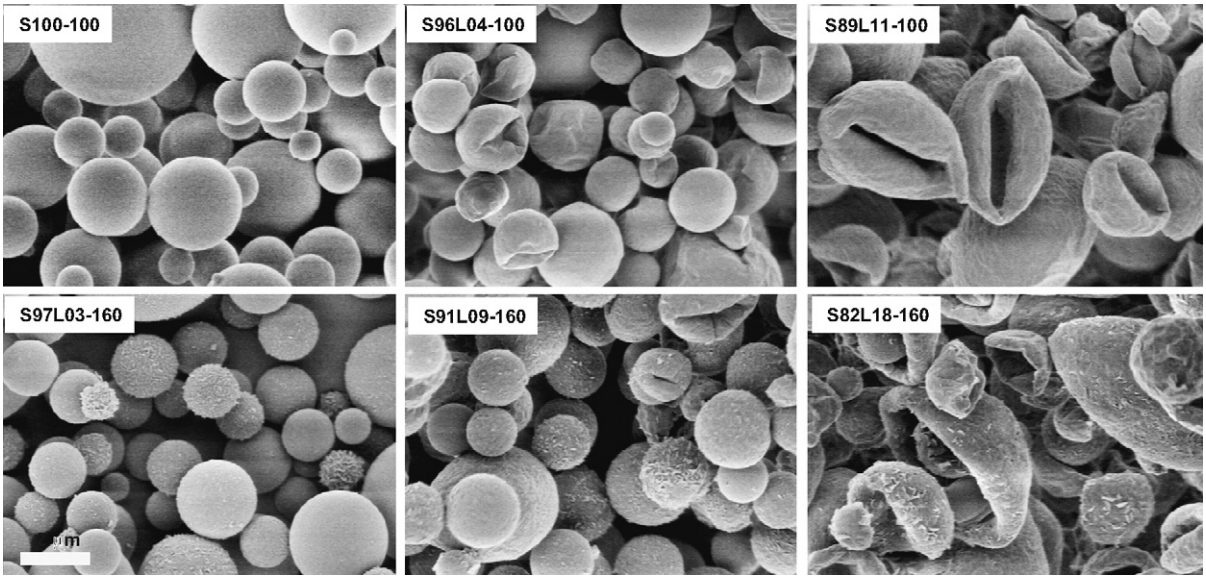

Fig. 2. SEM images of the uncoated and L-leucine coated salbutamol sulphate powders. Scale bar is 2 μm.

Table 2
Aerosolization characteristics of the carrier-free powder formulations. Experiments were conducted with Inhalation Simulator[45,46] using fast inhalation profile with the maximum inhalation flow rate of 67 l min^{-1}. Inhaler used was Easyhaler®. Abbreviations: S_{micr}, micronized salbutamol sulphate powder; S, salbutamol sulphate; L, L-leucine; ED, average emitted dose; CV_{ED}, coefficient variation of emission; FPF, fine particle fraction ($D \leq 5$ μm); MMAD, mass medium aerodynamic diameter; GSD, geometric standard deviation.

Sample	ED (mg/dose)	CV_{ED}	FPF (%)	MMAD (μm)	GSD
S_{micr}	1.9	0.14	14	3.7	1.2
S97L03-160	6.3	0.07	43	2.9	1.6
S91L09-160	5.5	0.09	43	2.7	1.8
S82L18-160	3.2	0.38	50	2.0	1.7

The aerosolization results of the carrier-free formulations are summarized in Table 2. Emitted dose (ED) of the coated powder decreased from 7.1 to 3.2 mg/dose along the increased L-leucine content and decreased particle density (see Table 1). However, the emission characteristics are suggested to be mainly governed by the morphology (wrinkled vs. sphere) and surface roughness (asperity size and density) of the particles. (One should note that the lactose carrier particles (Spherolac 100) that flow well showed the ED of 8.5–9.5 mg/dose.) Fine particle fraction (FPF) was reasonably high, 42–50%. Among the coated powders, S82L18-160 showed the lowest ED and density but the highest FPF and the coefficient of variation of emission (CV_{ED}). The micronized powder showed the lowest ED and FPF.

3.2.2. IGC measurements

Table 3 summarizes the IGC results. The parameters K_A and K_D describe acidic (electron acceptor) and basic nature (electron donor) of a surface. It is hypothesized; when K_A and K_D are equal the nature of the surface is amphoteric. The nature of the micronized powder was acidic and it performed the highest γ_S^D. The changes in γ_S^D and K_A/K_D are similar except in cases of S89L11-100 and S82L18-160 which showed strongly acidic surface. The surfaces of all the other L-leucine coated powders were amphoteric or slightly basic. When L-leucine molecule organizes at the air–water interface of a droplet its hydrophobic tail, *tert*-butyl, faces towards the air phase. This results in the formation of hydrophobic outer layer for the dry particles (Raula et al., 2008d). This subsequently should increase the hydrophobicity of the surface leading to the lowered γ_S^D. This is true when compared the powders S96L04-100 and S89L11-100 that were prepared at same temperature. The γ_S^D of S96L04-100, however, is much higher than that of S100-100. Chew et al. (2005) found no correlation between γ_S^D and L-leucine concentration and our sample number was too low to draw any meaningful conclusion. It is hypothesized that the carboxylic acid group of L-leucine in S89L11-100 and S82L18-160 is responsible for the increased acidic surface nature ($K_A/K_D > 1$). S_{micr} and S100-100, both being purely composed of salbutamol sulphate, showed opposite nature: S_{micr} was acidic and S100-100 basic. This is not surprising because it is well known that the processing conditions influence particle surface properties.

3.2.3. Discussion on surface energetics and aerosolization

Contact area and nature between the surfaces have crucial roles for the delivery of any powdery system but particularly of fine powders smaller than 10 μm. The dispersion of particle agglomerates requires aerodynamic shear stress to overcome agglomerate strength that is proportional to the work of adhesion between the particles. The surface roughness decreases the contact area and also increases the distance of separation. The asperities may, however, mechanically interlock adjacent particles resulting in the worsened the dispersion of a powder. In addition to particle-particle interaction, the particles should also overcome the adhesion force induced with an inhaler wall. The work of cohesion (W) decreases if the surface energy (γ) decreases and/or the contact area (A) between the adjacent surfaces decreases according to the equation $W = 2A\gamma$. It is also known that discontinuous domains such as edges, facets, corners and crystal defects are more energetic than flat surfaces (Bai et al., 1991; Patten, 1979).

In this study, the surface energy measurements were expected to reveal the true influence of surface nature on the aerosolization behaviour of the powders. As it was clearly observed, the surface topography, i.e. roughness was a crucial factor for aerosolization and, compared to that, the role of L-leucine as a surface material was minor. This is supported by the fact that the powder coated only with the surface-diffused L-leucine could not be delivered without the carriers. To obtain flowable powders, the particle surfaces needed to be coated by the PVD of L-leucine. For the PVD coated powders, no all-interpretative correlation between γ_S^D and ED, FPF, CV_{ED} or surface morphology was found.

Similarly, K_A/K_D and δ did not explain thoroughly the ED and FPF of the powders but a reasonably good correlation was observed with CV_{ED}. Accordingly, one may interpret that the worsened emission and dose repeatability of S82L18-160 seemed to be governed by the acidic surface nature whereas the improved dispersion by the low γ_S^D. These two parameters may also co-affect on aerosolization. The lowered emission may be attributed to the increased interaction between the powder and the delivery chamber walls of the inhaler. Thereby, it is hypothesized that this interaction may have an electrostatic origin to prevent the emission of S82L18-160. On the other hand, the lowered γ_S^D and the lowest density among the coated powders may explain the improved break-up of particle–particle interaction

Table 3
Surface properties of the powders. Symbols: γ_S^D, dispersive surface energy; ΔG_A^{SP}, surface free energy; K_A and K_B, acid and base constants. The regression standard deviation is shown in the brackets.

Sample	γ_S^D (mJ/m^2)	ΔG_A^{SP} (kJ/mol)				K_A	K_D
		Ethyl acetate	Acetonitrile	Acetone	Ethanol		
S_{micr}	40.00 (0.028)	7.44 (0.03)	9.35 (0.02)	6.14 (0.02)	7.86 (0.02)	0.095 (0.053)	0.065 (0.077)
S100-100	26.62 (0.032)	5.61 (0.01)	8.31 (0.03)	4.42 (0.06)	6.27 (0.05)	0.070 (0.000)	0.085 (0.177)
S96L04-100	34.56 (0.040)	6.90 (0.08)	9.81 (0.05)	6.52 (0.11)	6.52 (0.02)	0.090 (0.111)	0.090 (0.111)
S89L11-100	25.56 (0.131)	6.81 (0.12)	8.86 (0.09)	6.64 (0.10)	6.11 (0.12)	0.090 (0.111)	0.060 (0.000)
S97L03-160	32.68 (0.070)	6.68 (0.06)	9.20 (0.07)	6.04 (0.11)	6.32 (0.08)	0.090 (0.000)	0.090 (0.000)
S91L09-160	37.23 (0.028)	7.52 (0.07)	10.46 (0.03)	6.10 (0.02)	7.48 (0.03)	0.090 (0.111)	0.085 (0.294)
S82L18-160	26.52 (0.018)	5.80 (0.01)	7.37 (0.03)	5.05 (0.03)	4.68 (0.02)	0.080 (0.000)	0.035 (0.143)

and aerosolization performance, i.e. dispersion in the gas, respectively.

4. Conclusions

Salbutamol sulphate microparticles were surface-modified using amino acid L-leucine as a surface modifying agent. The drug particles were coated by L-leucine at varying saturation conditions in the gas phase. Accordingly, the surface topography of the particles varied from smooth (surface diffusion) to rough (physical vapour deposition). The aerosolization performances of the carrier-free powders were investigated and the effect of particle surface properties on the emission and dispersion of the powders attempted to reveal by surface energy parameter obtained by IGC. Only the fine powders with the PVD coating of L-leucine (crystalline chips on the particle surfaces) that possessed reasonable surface roughness could be delivered without the carrier particles. The delivery from the inhaler improved as the content of L-leucine on particle surfaces decreased. However, the emission characteristics are suggested to be governed by the morphology, surface roughness (asperity size and density) of the particles and acidity of the particle surface. Moreover, the dispersion behaviour of the powder with high L-leucine content was explained by the acidic surface nature that could have contributed to the particle detachment. Dispersive surface energy did not directly correlate with any of the aerosolization results. This work enlightened that the aerosolization of such coated powders is a complex matter that cannot be simply predicted using surface energy characteristics alone. To prepare well-flowable and -dispersible carrier-free fine powders requires one's attention to fine-tailor particle surfaces.

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