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Aerosolization behavior of carrier-free L-leucine coated salbutamol sulphate powders

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ABSTRACT

Aerosolization behavior of carrier-free L-leucine coated salbutamol sulphate inhalable powders has been studied. L-Leucine coatings were formed by physical vapour deposition (PVD) on the surface of the spherical particles in the gas phase. While depositing L-leucine formed pointy crystalline asperities whose size and density increased with the increased content of L-leucine in the gas phase. The asperity size changed from few nanometers to hundreds of nanometers. Due to the rough surface, all these coated fine powders were well-flowable and could be fed without the aid of coarser carriers. The aerosolization characteristics of the powders were studied with 'Inhalation Simulator' under ascending and fast inhalation profiles. When detected on-line by infrared light attenuation, the emission of the coated powders from an inhaler (Easyhaler®) was distinctively dependent on the inhalation flow rate less than 30 l/min whereas that of micronized salbutamol sulphate powder solely depended on the studied inhalation flow rate range up to 100 l/min. Gravimetric measurements showed that emitted doses (ED) and fine particle fractions (FPF) of the coated powders were 5.1–7.1 mg/dose and 42–47%, respectively, which were 3–4 times higher than those of the micronized powder. The ED and FPF of the coated powders decreased as the surface roughness increased which is hypothesized as mechanical interlocking between the surface asperities.

1. Introduction

In inhalation delivery, the effective transportation of fine drug powders deep into the lungs requires to overcome particle agglomeration, induced mainly by van der Waals but also electrostatic and capillary interactions between particles. Such interacting forces determine the flowability and dispersibility of a powder (Zeng et al., 2001; McGlinchey, 2005). The particles within a respirable size range of 1–3 μm are difficult to handle as such in an accurate manner due to the increased attraction forces between the particles (Gonda, 1981; Hickey et al., 1994). Thus, the carriers with size of 60–100 μm are needed for an accurate dosing of drugs into the lungs. However, the carriers may inflict problems on patients who are, for instance, intolerant to carrier material such as lactose. In such case, carrier-free formulations would be advantageous. Some carrier-free formulations in the market base on inhaler technology to disperse micronized powders. These inhalers include dry powder inhalers (DPI) Turbohaler™ (Wetterlin, 1988) and Twisthaler™ (Tang and Kenyon, 2000) where loosely agglomerated micronized drug particles are dispersed in a high turbulent flow inside the inhaler. A different type of carrier-free formulation is Exubera® where the insulin particles that are spray-dried are delivered by Turbohaler™. Usually, the spray-dried powders must be delivered with the carriers regardless of inhaler type but in this particular case the powder performance relied on the properties of insulin to reduce the interacting forces between particles. Hence, to optimise the powder delivery it is utmost important that in parallel with to the inhaler development the powder formulations whose delivery characteristics are independent of inhaler type and respiration are developed.

Several approaches to improve the aerosol properties of fine powders include the use of fine and coarse carrier particles (Lucas et al., 1998; Zeng et al., 2000), the modification of surface characteristics (Chew and Chan, 2001; Fults et al., 1997), lowering particle density (Ben-Jebria et al., 1999) and the incorporation of excipients (Hanes et al., 1997). The surface-modifying expicients act as lubricants between surfaces thus improving flowability and dispersibility of powders (Staniforth and Morton, 2002; Zeng et al., 1998). One class of such excipients is amino acids that improve aerosol properties of powder (Staniforth, 1996, 1997; Ganderton et al., 2000; Lucas et al., 1999). For example, a powder formulation containing at least two leucyl residues provide a highly dispersible aerosol formulation (Lechuga-Ballesteros and Kuo, 2001). When carrier-free formulations are in question a crucial task is to

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overcome the cohesion forces between fine particles. These forces can be reduced by engineering of particle shape and surface texture and by a choice of surface material. A curved surface with small asperities and low surface energy has proved to be particularly effective, due to reduction of the contact area between adjacent surfaces (Israelachvili, 1991; Podczeck, 1999; Li et al., 2006). The modification of particle surfaces has been achieved by the incorporation of material known to lower attraction forces. In the co-spray drying, the formation of a coating layer depends on surface affinity of a molecule (Lechuga-Ballesteros and Kuo, 2001; Li et al., 2003, 2005a,b). In the powder blending (Zeng et al., 1998; Staniforth and Morton, 2002; Lucas et al., 1998) the mechanical processing presumably induces electric charging. The coating layer has been also prepared by has been the physical vapour deposition (PVD) of a coating agent on particle surfaces. This is conducted in fluidized bed reactors where particle size is limited to larger than approx. 10 μm to deagglomerate particles prior to the coating (Chungi and Iorio, 2004).

We recently demonstrated a novel gas-phase coating method that can be employed on single particles and is independent of the size of particles to be coated (Raula et al., 2007a, 2008a,b; Lähde et al., 2008). In this method the drug particles and coating layer are formed consecutively starting from a single precursor solution. The coating layer was formed by the physical vapour deposition (PVD) of amino acid L-leucine on the surface of the spherical drug particles of salbutamol sulfate in an aerosol flow reactor. During vapour deposition, L-leucine formed crystals of a few nanometers on the surface of individual drug particles. These powders showed excellent flowability and dispersibility performance even without the aid of carrier particles.

Using this gas-phase coating method, we have prepared several L-leucine coated inhalable salbutamol sulphate powders where the number, size and density of L-leucine crystals on particle surfaces varied. These powders were subjected to the dispersion studies conducted with an apparatus called '*Inhalation Simulator*' developed in-house (Kurkela et al., 2002; Kauppinen et al., 2002). This apparatus allows one to control inhalation flow profile to mimic, for instance, the respiration of a child or healthy adult man. The apparatus induces the actual inhalation flow caused by a patient through the dry powder inhaler and records on-line the powder emission. Recently, Martin et al. (2006, 2007) introduced a method of laser diffraction to study the agglomerate size of powder emitting from Turbohaler™ This fine method, however, lacks when using inhalers whose operating mechanism do not break up the agglomerates in a vigorous manner inside the inhaler. An example is Easyhaler® that does not possess any mechanistic features to disperse powder inside the inhaler thus allowing studying the actual performance of a powder itself.

We aimed to explore the aerosolization characteristics of the carrier-free formulations of the novel L-leucine coated powders under two distinctively different inhalation profiles, i.e. fast and ascending profiles. Particular interest has been put on the influence of surface roughness, i.e. the size and density of crystalline L-leucine asperities on powder flowability and dispersibility.

2. Materials and methods

2.1. Preparation of L-leucine coated particles

2.1.1. Materials

Salbutamol sulphate (Alfa Aesar, Germany) and L-leucine (Fluka, Switzerland) were used as received. The materials were dissolved in deionized water (pH 6; Millipore) to give precursor solutions where the concentration of salbutamol 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 (Eerikäinen et al., 2003; Raula et al., 2004; Lähde et al., 2006) 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 (±0.1) l/min, 22 °C) to the reactor consisting of five stainless steel tubes (i.d. 3 cm, length 120 cm). Reactor temperature was 190 °C (±1 °C). At the reactor downstream the aerosol was rapidly cooled with N_2 gas (22 °C) at 80 l/min in a porous stainless steel tube (i.d. 3 cm, length 20 cm). The aerosol flow became turbulent with a Reynolds number over 3000. The cooling rate from 190 to 30 °C was 2.2 °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 as used in this work.

2.2. Dispersion experiments

2.2.1. Powders

The L-leucine coated powders and commercial micronized salbutamol sulphate powder, S_{micr} (a gift from Gamprex, Italy) were used for the dispersion testing as received. All the fine 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 behavior 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 carriers) 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 emission is detected on-line by a light attenuation between two opposing IR probes lined at the exit of the inhaler and also gravimetrically using a low pressure impactor. Inhalation run was performed 10 times in between the inhaler was knocked 3 times vertically as an upright position on the table prior to the dose loading and inhalation.

2.2.3. Inhalation profiles

Two inhalation profiles, fast inhalation (Fig. 1a) and ascending inhalation (Fig. 1b) were employed:

1. *Fast inhalation*: The inhalation flow rate changed abruptly from 0 to 63 l/min (±1 l/min) in 2 s and then maintaining this flow rate for 9 s. The inhalation was initiated after 1 s from the beginning of the experiment. 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 flow the flow deaccelerated with 53.2 l min^{-1} s^{-1} and 5.8 kPa s^{-1}.
2. *Ascending inhalation*: The inhalation flow rate increased from 0 to 100 l/min with a flow acceleration of 5.5 l min^{-1} s^{-1} within 17.5 s. Accordingly, the pressure increased in a convex manner up to 17.4 kPa. No deaccelerating part exists but inhalation was stopped abruptly as the flow rate reached the maximum target value.

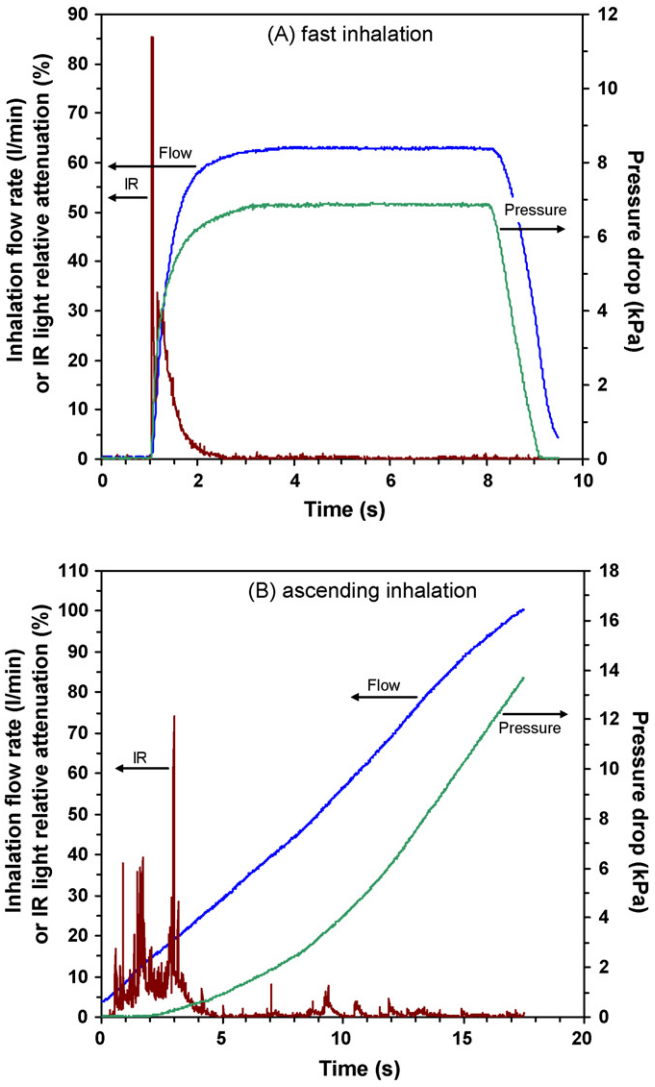

Fig. 1. Inhalation profiles employed for the dispersion experiments of the carrier-free powder formulations: (a) fast and (b) ascending inhalations.

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). Geometric number mean diameter (GNMD) and geometric standard deviation (GSD) of the size distribution were determined assuming that the density of the particles was 1 g/cm^3. In ELPI, an oiled porous collection of 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).

2.3.2. Powder dispersion

Powder emissions detected by IR light attenuation were reported as cumulative attenuation (ATT_{CUM}) as a function of inhalation flow rate (ascending inhalation) or as a total attenuation upon the inhalation (fast inhalation).

The dispersed fine particles were collected isokinetically at the downstream of Inhalation Simulator by a Berner-type low pressure impactor, BLPI (Hillamo and Kauppinen, 1991) with a stage aerodynamic cut-off diameters ranging from 0.03 to 15.61 μm. 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

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

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

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).

3. Results and discussion

3.1. Powder characteristics

3.1.1. Particle morphology

Fig. 2 shows the SEM images of the micronized salbutamol and the L-leucine coated salbutamol particles. As seen, the micronized drug particles were faceted. These non-uniform and elongated particles, when in an intimate contact, usually lead to a large contact area between the particles. Such fine powders are usually very cohesive and perform poor flowability and hence their delivery via an inhalator is assisted with a coarser carrier powder. The L-leucine coated powders were spheres having the coating layer composed of small leafy-looking L-leucine crystals of a few nanometers (Raula et al., 2007a, 2008a,b). The size of crystals pointing out particle surfaces grew with added L-leucine. The size of asperities was attempted to determine by atomic force microscope (AFM) but this failed due to fragile L-leucine crystals. Thus, the asperity size and their density were visually observed by SEM: the size and likely density of the asperities increased along the increasing concentration of L-leucine. The amount and size of the crystals varied in the sample, i.e. L-leucine did not deposited evenly on each particle. One reason could be that fractions of L-leucine vapour in a parabolic flow experienced the cooling phenomenon differently depending on its position relative to the entry of the cooling gas. Another explanation stands for the knowledge that the growth-rate of particles via heterogeneous nucleation increases with decreasing size of core particles according to the relation $dD_p/dt \sim 1/D_p$ (Flagan and Seinfeld, 1988). To our knowledge, a liquid form of L-leucine at ambient pressure has not been reported. Thus, gaseous L-leucine molecules transform directly to solid form and simultaneously crystallize while nucleating on core particle surfaces. Such a PVD process favours for gaseous species to nucleate on the discontinuous sites such as edges and corners of the core particles as it demonstrated in our previous work (Raula et al., 2008b).

3.1.2. Powder composition

The nucleation of L-leucine vapour takes place not only on the surface of salbutamol core particles (heterogeneous nucleation)

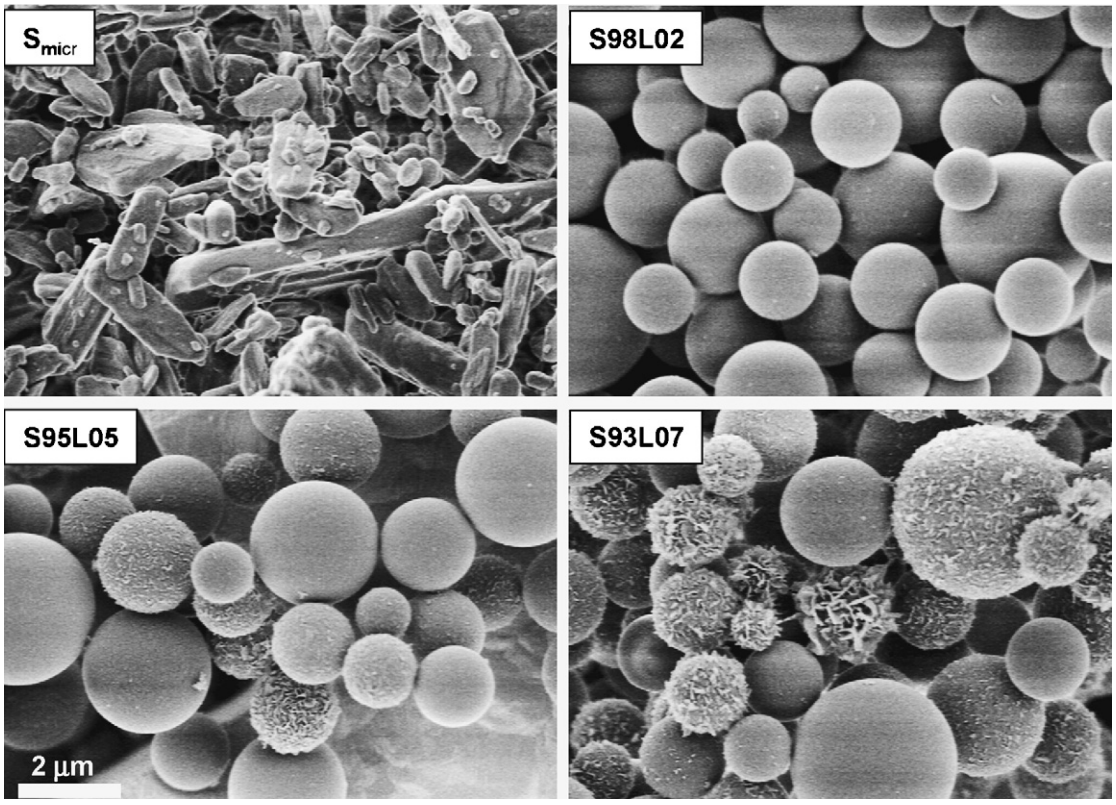

Fig. 2. SEM images of the micronized salbutamol sulphate powder and the L-leucine coated salbutamol sulphate powders.

but also by itself to form pure L-leucine particles (homogeneous nucleation). The magnitude of the latter nucleation mode depends on the extent of L-leucine sublimation (Raula et al., 2007a; Raula et al., 2008a). In this study, all L-leucine sublimed and thus the coating was purely formed by PVD. We have proved earlier by X-ray and electron diffractions that L-leucine crystallizes upon vapour deposition (Raula et al., 2007a). These crystals preferred the crystallographic orientation of (−1 1 0) in addition to the (0 0 1) direction when compared with that of bulky L-leucine crystals. As it is shown in Table 1, the amount of L-leucine in the drug powders was distinctively lower (approx. 75–79%) than in the precursor solutions. One cause to this is the minor vapour/particle losses on the reactor walls. The losses were not measured. However, the major fraction of the 'disappeared' L-leucine fraction formed pure L-leucine particles via homogeneous nucleation (Raula et al., 2007a). Their size was smaller than the cut-off size (0.7 μm at 90 l/min) of the cyclone leading to these particles to be removed upon powder collection. The size distributions of the pure L-leucine particles were subtracted from the overall size distributions to give the distributions of the coated salbutamol particles whose size (GNMD) varied between 1.6 and 1.8 μm and GSD between 1.6 and 1.9.

Table 1
Precursor solution and powder characteristics

Sample	Precursor solution			Produced powder	
	C_{total} (g/l)	S (wt.%)	L (wt.%)	S (wt.%)	L (wt.%)
S98L02	32.5	92	8	98	2
S95L05	37.5	80	20	95	5
S93L07	45.0	67	33	93	7

Abbreviation: S, salbutamol sulphate; L, L-leucine; C_{total}, total precursor solution concentration.

In the earlier study with LC–MS we found that salbutamol sulphate degraded in the powder production at 190 °C (Raula et al., 2008c). It was proposed that the *tert*-butyl group of salbutamol sulphate was cleaved to make the residual molecule very hygroscopic. In the present study, however, the degradation products are not expected to influence the dispersion of the coated powders although it is known that the powder behavior could be affected by many physical parameters. The focus in this study was to explore the influence of L-leucine surface roughness on dispersion behavior.

3.2. Aerosolization experiments

3.2.1. On-line monitoring of powder emission

It should be reminded that the dispersions of the fine drug powders were studied without the use of the carrier particles. Thus, the emission and dispersion originate exclusively from the properties of the fine powders. The delivery of powder from the inhaler has been detected using the IR probes as described above. This is a crucial tool for the on-line monitoring of powder emission under inhalation. Fig. 1a and b shows typical changes in the light attenuation between the IR probes during the ascending and fast inhalations. The fast inhalation resulted in the removal of fine powder within 2 s from the onset of the inhalation. It was observed that the IR attenuation changed in two distinctive steps during the fast inhalation. High inhalation flow rate probably induced powder recirculation at the exit of the inhaler mouthpiece. This recirculation was not in the focus of this work and thus not studied further. When the ascending flow rate was employed the major fraction of the fine powder removed from the inhaler within the first 5–6 s.

3.2.1.1. Ascending inhalation. Figs. 3 and 4 present the normalized cumulative IR attenuations (ATT_{CUM}) and corresponding variation coefficients (CV_{ATT}) of the emissions. Actual cumulative attenua-

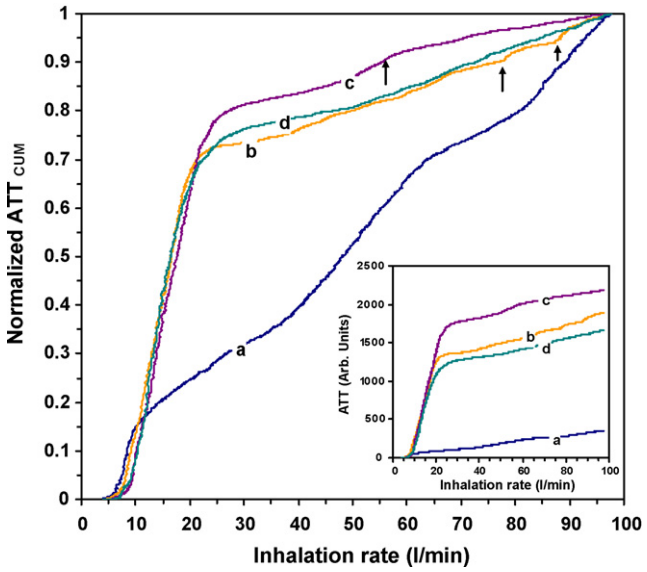

Fig. 3. Emissions of the powders (a) S_{micr}, (b) S98L02, (c) S95L05 and (d) S93L07 recorded as cumulative IR light attenuations (ATT_{CUM}) upon the ascending inhalation. The main figure shows the normalized ATT_{CUM} and the inset the original attenuations. Arrows guide the eye to find the inhalation flow rate related jumps in ATT_{CUM}.

tions recorded during the inhalation are shown in the inset of Fig. 3. The S_{micr} powder performed distinctively lower emission than the coated powders among which S95L05 showed the best emission. Within 0–30 l/min the ATT_{CUM} of the coated powders increased rapidly to 74–82% whereas that of S_{micr} increased gradually to be only 32%. Above 30 l/min the ATT_{CUM} of the coated powders increased was gradual but one may observe that the ATT_{CUM} curve changed in small jumps at a certain flow rates. This implied that the emission of a powder was dependent on a reached inhalation rate to 'trigger' the emission of powder of a certain amount. However, the emissions varied between the repetitions. This is attributed to a dose repeatability that could be evaluated by the variation coefficient of the IR attenuations, see Fig. 4. All the powders showed very large emission variation (CV_{ATT} » 1) at low flow rates of less than

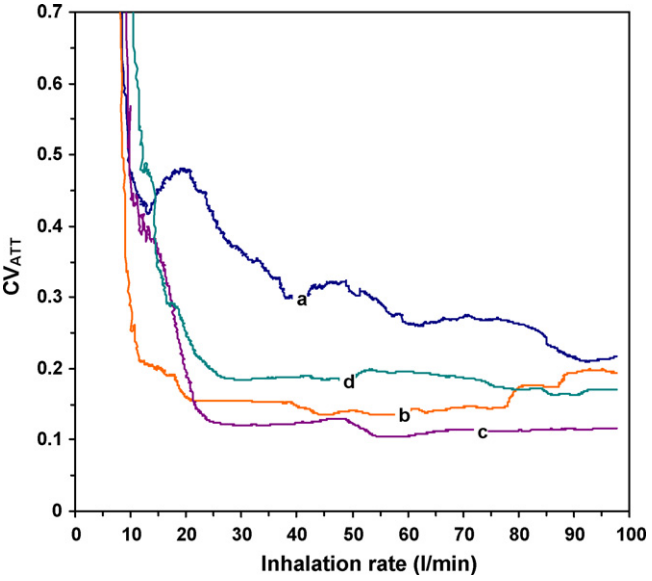

Fig. 4. Variation coefficients of the cumulative IR light attenuations of the powders (a) S_{micr}, (b) S98L02, (c) S95L05 and (d) S93L07 upon the ascending inhalation.

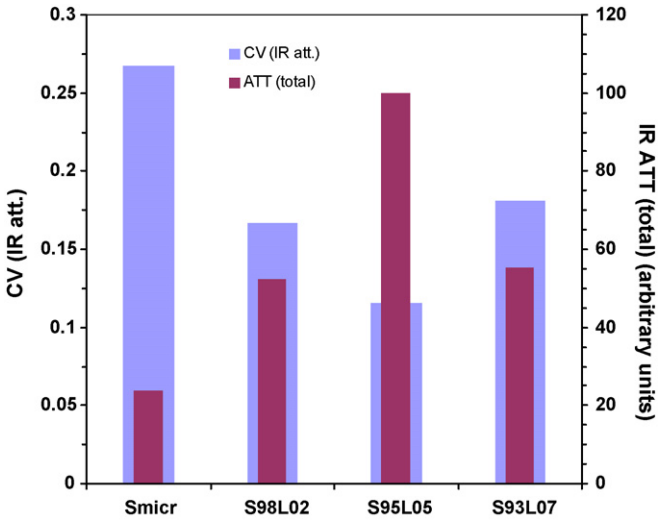

Fig. 5. Total IR light attenuations of the powder emissions and their variation coefficients upon the fast inhalation.

10 l/min. Upon the increase of the flow rate from 15 to 100 l/min, the CV_{ATT} ranged from 0.1 to 0.5 where the micronized powder showed the highest and S95L05 the lowest CV_{ATT}. Jump-like changes in the variations as a function of flow rate correlated well with those of the ATT_{CUM} curves. This implied that the changes were very much related to the characteristics to the powders. Accordingly, one may interpret that the dependence of the powders on the inhalation flow rate increased in order of S95L05 < S98L02 < S93L07 < S_{micr}.

3.2.1.2. Fast inhalation. The emissions of all the L-leucine coated powders took place within 2 s from the onset of the inhalation. The major part of the micronized powder, approx. 90% of the total attenuation, was emitted within the first 2 s and the rest of powder was emitted during 1 s as observed as an additional change in attenuation. Fig. 5 brings to the comparison the IR attenuations (average of 10 emissions) and corresponding variation coefficients. Interestingly, the dose emission and variation showed opposite tendency, i.e. the variation (dose repeatability) increased when the emission decreased, and vice versa.

3.3. Gravimetric measurements

Table 2 summarizes the results of the gravimetric measurements of average emitted doses (ED) and their variation coefficients (CV_{ED}) and fine particles fractions (FPF). Noteworthy, the ED and CV_{ED} between the samples were similar with the ATT_{CUM} and CV_{ATT} except in the case of S98L02. One should note that IR and gravimetric measurements observe different phenomenon: IR detection is proportional to r^2 whereas the mass measurement to r^3, where r is the radius of the object such as particles and agglomerates. The IR detection is valid if scattering is linear according to a projected area. It is expected to be linear in this study. Thus, the behavior of S98L02 would mean that the IR light attenuation is not only a measure of efficiency of emission but is also related to deagglomeration of powder inside the inhaler. In this case, the increased agglomerate size would attribute to increased attenuation and increased emitted dose. These two parameters may contribute simultaneously to the light attenuation which complicates the interpretation. The agglomerate size could be determined by laser diffraction but this method was not available in this study. However, the comparison with the gravimetric results reveals the behavior of a powder: the attenuation may be low even though the ED is high because

Table 2
Dispersion results of the carrier-free formulations upon the fast and ascending inhalations

Sample	Fast inhalation, Q_{max} 63 l/min					Ascending inhalation, Q_{max} 100 l/min	
	ED (mg)	CV	FPF (%)[a]	MMAD (μm)	GSD	ED (mg)	CV
S_{micr}	1.9	0.14	14	3.7	1.2	2.1	0.16
S98L02	7.1	0.11	47	1.9	1.7	7.1	0.16
S95L05	6.2	0.11	46	3.1	1.8	6.4	0.08
S93L07	5.1	0.16	42	2.9	1.7	5.1	0.07

Abbreviations: S_{micr}, micronized salbutamol sulphate powder; ED, average emitted dose; CV, variation coefficient; FPF, fine particle fraction; MMAD, mass medium aerodynamic diameter; GSD, geometric standard deviation; Q_{max}, maximum inhalation flow rate.
[a] Standard deviation ±3%.

the powder disperses well already inside the inhaler. Accordingly, the deviation in the case of S98L02 is understood as the emission of smaller agglomerates than the rest of the powders. Respectively, S98L02 deagglomates better in the very beginning of the inhalation that can influence powder dispersion in general.

The EDs of the coated powders were relatively high 5.1–7.1 mg/dose being approx. 60–70% of that of the commercial lactose carrier powder (Spherolac 100, size approx. 100 μm) as tested in this work. Since the removal efficiency vs. the loaded dose could not be estimated it was expected that all the powder that was loaded was removed from the inhaler upon the ascending inhalation. Accordingly, the emission was an indirect method to estimate the loading efficiency, i.e. flowability of the powders. The fast inhalation emptied the loaded sample with the high ED yield of 90–100% in relation to that gained upon the ascending inhalation. The coated powders showed the FPF of 42–47% that were around 3 times higher than that of S_{micr}.

3.4. Effect of surface asperities

Fig. 6 aims to correlate the obtained results relative to the size and density of L-leucine asperities (L-leucine content) on the particle surfaces. First of all, S_{micr} performed poor flowability (low ED), dispersibility (low FPF) and repeatability (high CV_{ED}) when compared those of the coated powders. Among the coated powders, the emission worsened with the added L-leucine (Table 2). With the highest content of L-leucine and thus the largest surface asperities the dispersion worsened only slightly but the repeatability worsened notably: the CV_{ED} of S93L07 was even higher than that of the S_{micr}.

The dispersion of the fine powders blended with carrier particles has been shown to enhance with the added L-leucine. We have also reported that fine drug particles where L-leucine surface layer has been formed by a method of droplet-drying improved the dispersion (Raula et al., 2007b) where L-leucine diffused on droplet surfaces prior to the drying forming the coating layer for the particles. One should keep in mind, however, that the flowability and dispersibility of a powder are governed not only by the surface material but essentially by particle shape and surface roughness, that is, the size and density of surface asperities (Rabinovich et al., 2000; Katainen et al., 2006). For instance, the dispersion behavior of the fine powders where L-leucine coating is formed by the

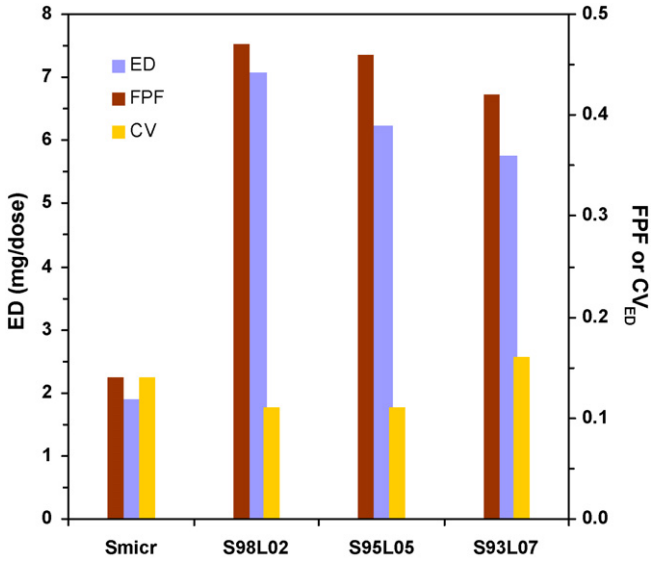

Fig. 6. Emitted doses and their variation coefficients and fine particle fractions (FPF, $D \leq 5$ μm) of the fine powders upon the fast inhalation.

surface diffusion cannot be examined without the aid of carrier particles due to very poor flowability. Moreover, the S_{micr} particles had non-uniform and elongated structure. If these particles are in an intimate contact, the contact area as well as attraction forces between the particles increase. Ideal particle shape is spherical. Surface asperities improve the particle distance of separation but the adhesion forces increase when the asperity size and density increase above certain limits and the rough surface starts to behave like a flat surface (Katainen et al., 2006). van der Waals attractions have been reported to be unsubstantial when the asperity size was of the order of 1 μm (Visser, 1989).

Fig. 7 illustrates the particles in surface contact studied in this work. As it was seen, the S_{micr} powder showed poor dispersion characteristics most probably due to increased contact area. The L-leucine coated powders were spherical with the rough surface texture. Unfortunately, the asperity size of the coated powders could not be measured accurately but as it was observed by SEM these parameters increased simultaneously as the amount

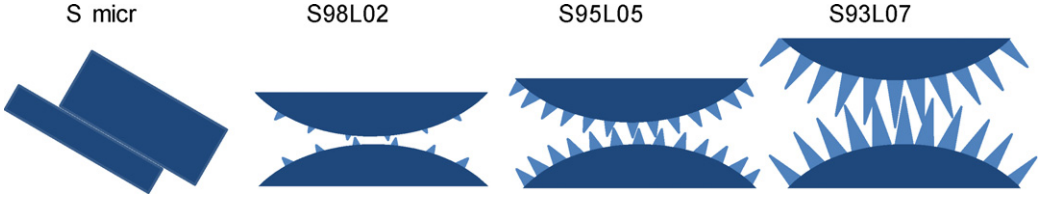

Fig. 7. Illustrations of particle contacts studied in this work. The highest contact area is induced with the micronized powder. The distance of separation increases as the size of the L-leucine asperities increases. The particles may be mechanically interlocked along the increasing asperity size.

of L-leucine increased. The surface of pharmaceutical solids usually contains different-sized asperities that can interlock particles (Packham, 2003). As a consequence, the contacting area increases thus increasing the interaction between the particles. Although the separation of the particles increases, the mechanical interlocking becomes pronounced when the surface becomes rougher. As it was observed from the results, the ED and FPF decreased along the increasing size of L-leucine asperities. The asperity size and likely density were the lowest in the case of S98L02 which showed the best flowability, emission and dispersion characteristics. Particularly, the sample with largest asperities S93L07 showed not only lowered loading/emission and dispersion but the dose repeatability was worse than those of the other coated powders. This was assumed to be a result of the mechanical interlocking between the asperities.

4. Conclusions

Aerosolization behavior of the carrier-free formulations consisting of inhalable salbutamol sulphate particles coated with L-leucine crystals has been studied under fast and ascending inhalation profiles. Varying amounts of coating on the surface of the powders were accomplished by the physical vapour deposition of L-leucine. Upon deposition, L-leucine formed pointy crystals whose size and density increased with the amount of L-leucine. The performances of the coated powders such as the powder emission from the inhaler and fine particle fraction were 2–3 times that those of the micronized salbutamol powder. Under the ascending inhalation flow rate the coated powders showed excellent emission even at low flow rates less than 30 l/min whereas the emission of the micronized salbutamol powder was notably dependent on the applied flow rate. When the size and density of surface asperities (L-leucine crystals) increased the emission and dispersion of powders lowered. This was assumed to be a result of the mechanical interlocking between the asperities as their size increased. This study highlighted the aspects of particle shape and particularly surface asperities when developing carrier-free inhalable drug formulations.

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