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Short Communication

A Novel Gas Phase Method for the Combined Synthesis and Coating of Pharmaceutical Particles

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Purpose. A novel aerosol flow reactor method for the combined gas phase synthesis and coating of particles for drug delivery has been developed.
Materials and Methods. As an example, micron-sized salbutamol sulfate particles were produced via droplet-to-particle conversion and in-situ coated by the physical vapor deposition (PVD) of L-leucine vapor.
Results. During the deposition, L-leucine vapor crystallized on the surfaces of amorphous salbutamol particles. The size of L-leucine crystallites increased with increasing vapor concentration of L-leucine. The salbutamol particles with rough L-leucine surfaces exhibited good flowability enabling to them to be dispersed into air flow without the delivery aid of coarse lactose carriers.
Conclusions. The fraction of particles smaller than 5 micrometers varied between 0.35 and 0.48 when dispersed into 60 l/min air flow having a jet Reynolds number of 30700. When the coated fine particles were blended with lactose carriers, the fine particle fraction was as high as 90%. The L-leucine coating also improved the stability of salbutamol particles when stored at 45% relative humidity atmosphere.

KEY WORDS: aerosol; coating; evaporation; gas phase deposition; inhalation; L-leucine; pharmaceutical; powder production; salbutamol sulfate; surface modification; vapor.

INTRODUCTION

Flowability and dispersibility are important properties of powders for successful use in solid dosage formulations delivered, for instance, from dry powder inhalers (17). Adhesion and cohesion forces depend on particle size and on the contact area between particles. The reduction of surface forces, for instance by reducing the contact area between surfaces, commonly improves flowability and dispersibility. A curved, rough and hard particle surface has been proved to be effective (6,9,11,17).

Approaches to modify particle surfaces include, for instance, the blending of drug particles with fine particle expicients, such as lactose, magnesium stearate, phospholipids and L-leucine. These expicients act as lubricants between surfaces, thus improving flowability (16,13). In spray drying methods, the particle surface is formed during the drying of droplets. A good example of surface modification via spray drying is the use of surface-active amino acids, particularly leucine analogs, to reduce surface forces as they are enriched on particle surfaces (2,8,10). Attempts have been made to produce modified surfaces by an encapsulation technique in supercritical carbon dioxide (15) and by spray-coating (14) or by physical vapour deposition, PVD, (3) of particles in fluidized bed reactors.

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The existing surface coating methods have drawbacks. A discrete coating layer is desired i.e. the coating layer should provide solely surface properties for particles and not interact with core material. In many cases, however, individual particles cannot be coated because of strong attractive forces between such particles. Consequently, most probably unevenly distributed coatings would be found on the surface of agglomerates. In contrast, in the spray drying process a coating layer is formed during the drying of droplet. Droplets dry fast when the drying time needed for some molecules to fully diffuse onto the droplet surfaces prior to drying is not sufficient. Thus, the coating layer may not be discrete and does not necessarily provide the desired surface properties. In addition, the residence time will probably be too short to crystallize the surface layer.

We present a novel, one step process to synthesize and simultaneously coat particles in the gas phase with an aerosol flow reactor method. This is an in situ process where droplets containing both coating and active materials are first slowly dried, followed by the evaporation of coating material which subsequently coats solid aerosol drug particles via PVD. An amino acid L-leucine is evaporated, followed by deposition on the surface of the drug particles of salbutamol sulfate in a laminar aerosol flow reactor. L-leucine sublimes approximately at 145–148°C (1). During vapor deposition, L-leucine forms a discrete crystalline surface layer around individual drug particles. This gas phase coating method can be applied to diverse solid particles of different sizes, shapes and states i.e. amorphous or crystalline particles.

MATERIALS AND METHODS

Salbutamol sulfate (Alfa Aesar, Germany) and L-leucine (Fluka, Switzerland) were used as received. Precursor solutions contained 30 g/l of salbutamol and from 0 to 7.5 g/l of L-leucine dissolved in ion-exchanged water (pH 6). Lactose carrier powder, Spherolac 100 (Meggle Pharma, Germany), with an average size of 100 μm and micronized salbutamol sulfate (a gift from Cambrex Profarmaco, Italy) were used for the dispersion testing as received.

The preparation of coated particles with the aerosol flow reactor method (4,12) consists of droplet generation, particle drying, and the partial evaporation followed by deposition of a coating material on the surface of drug aerosol particles. Droplets were generated using an ultrasonic nebulizer (Pyrosol 7901, RBI, France) and transferred with the aid of dry nitrogen gas into a laminar flow reactor (stainless steel, id 30 mm, h 800 mm) that was at 180°C. Liquid volume consumption was 4×10^{-4} l/min with a gas flow rate of 1.5 l/min. The average residence time of the aerosol in the reactor was 16 s. Downstream of the reactor, the dry aerosol particles were cooled and simultaneously diluted in a porous tube (stainless steel, id 30 mm, h 200 mm) with a volume ratio of 26 (Reynolds number >3000). During the cooling and mixing, L-leucine vapor became supersaturated and deposited on salbutamol particle surfaces.

The number based size distributions, geometric number mean diameters (GNMD) and geometric standard deviation (GSD) of particles in the gas phase were determined with an electrical low-pressure impactor, ELPI (Dekati LTD., Finland). Mass based size distributions, and accordingly the mass median aerodynamic diameter (MMAD) and GSD of the dispersed particles were determined with a Berner-type low-pressure impactor, BLPI (5). Particles were imaged with a scanning electron microscope, SEM (Leo DSM982 Gemini, LEO Electron Microscopy Inc., Germany). The crystallinity of L-leucine coating was investigated with a transmission electron microscope, TEM (Philips CM-200, FEG/STEM, The Netherlands). Surface analysis was conducted with an X-ray photon spectroscopy, XPS (AXIS 165). Chemical identity of the compounds before and after particle production as well as powder compositions was examined by a nuclear magnetic resonance spectroscopy, NMR. Proton NMR measurements were conducted with a 200 MHz Varian Gemini 2000 spectrometer using deuterated water as a solvent. Powder quantities sufficient for dispersion testing were collected by a small-scale cyclone (18). Dispersion tests were conducted with a novel deagglomeration device at 15 and 60 l/min flow rates i.e. with jet Reynolds numbers of 7700 and 30700 (7). When testing was conducted with lactose carrier particles, 1.5 w-% of fine, coated salbutamol sulfate powder was blended with carriers in a stainless steel container for 10 min.

RESULTS AND DISCUSSION

Fig. 1a shows the SEM image of pure salbutamol particles that are amorphous spheres with GNMD of 1.01 μm and GSD of 2.2. During vapor deposition, L-leucine formed leafy-looking crystalline asperities on the surface of the salbutamol particles (Fig. 1b and c). The size of the asperities pointing out of the surface increased with the increasing vapor concentration of L-leucine. Surface analysis by XPS showed over 90 w-% surface coverage of L-leucine in all the L-leucine containing particles. The coated particles contained L-leucine 0.5, 2.0 and 5.0 w-% corresponding to L-

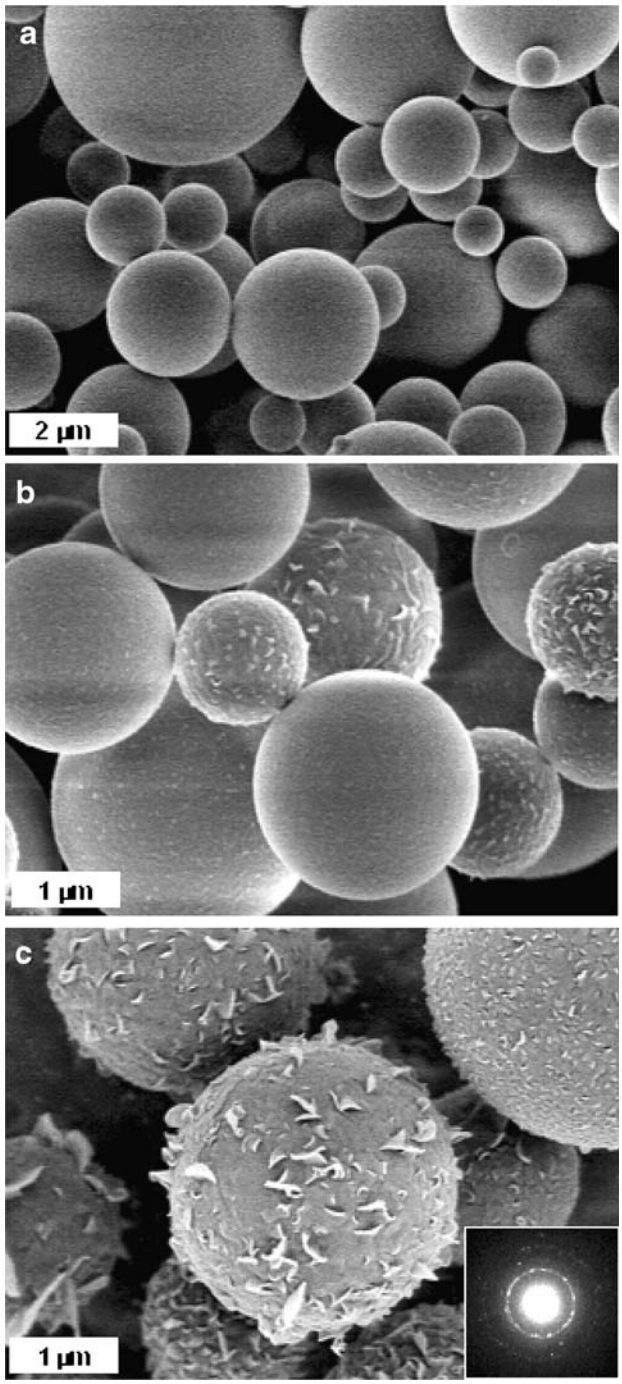

Fig. 1. SEM images of the produced salbutamol particles coated with different amounts of L-leucine, i.e. when varying the L-leucine concentration in the precursor solution: **a** salbutamol 30 g/l and no L-leucine, **b** salbutamol 30 g/l and L-leucine 2.5 g/l, and **c** salbutamol 30 g/l and L-leucine 7.5 g/l. The concentrations given are in the precursor solutions prior to particle preparation. The diffraction pattern of the L-leucine crystalline coating is shown in an inset as recorded with TEM.

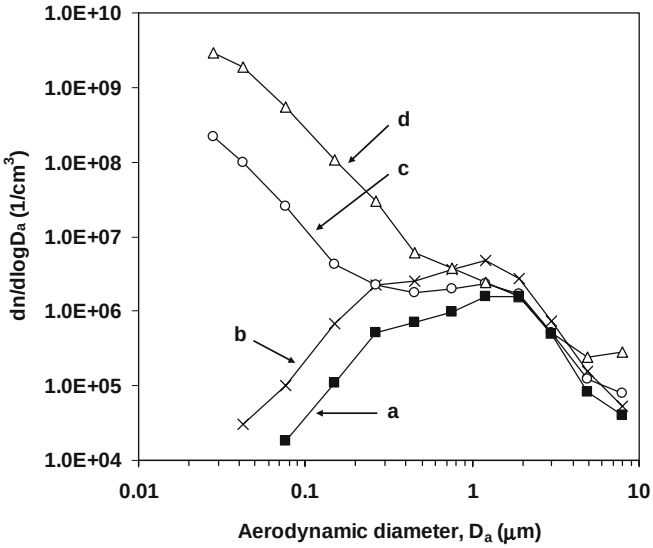

Fig. 2. Number size distributions of the produced salbutamol particles coated with different amounts of L-leucine. Samples: **a** salbutamol 30 g/l and no L-leucine, **b** salbutamol 30 g/l and L-leucine 1.0 g/l, **c** salbutamol 30 g/l and L-leucine 2.5 g/l, and **d** salbutamol 30 g/l and L-leucine 7.5 g/l. The reactor wall temperature was 180 °C.

leucine concentration of 1.0, 2.5 and 7.5 g/l in the precursor solutions, respectively. Moreover, the both compounds were stable under experimental conditions i.e. no molecular degradation was observed.

Fig. 2 shows the number size distributions of the uncoated salbutamol particles and L-leucine coated salbutamol particles produced at three different vapor concentrations of L-leucine. Apart from depositing on the salbutamol particles, the excess of L-leucine vapor nucleated homogeneously forming submicron particles whose number concentration increased with the increasing vapor content of L-leucine.

The dispersion testing was conducted with the deagglomeration device (7). Powder was fed in a continuous manner to the zone of turbulent flow intending to break up powder agglomerates. In this system of powder feeding, it is required that the powder that is fed with a flow rate 0.26 l/min has a sufficient flowability not to clog a feeding needle (ID 1.2 mm). As it was also visually observed, all the L-leucine coated particles flowed well and they could be fed as such without coarse lactose carriers. Instead, the uncoated particles and micronized particles were clumpy and clogged the feeding system. All the coated powders dispersed notably well at dispersing flow rates of 15 and 60 l/min resulting in fine particle fractions (FPF, $D \leq 5$ μm) between 0.35 and 0.48, MMADs between 1.7 and 2.4 μm, and GSDs between 1.6 and 1.9 (Table I). When the powders were fed from the blend of lactose carriers, the L-leucine coated particles resulted in high FPF values from 0.70 to 0.90 at a dispersing flow rate of 60 l/min. The FPF for the micronized salbutamol particles was merely 0.18 and for pure salbutamol particles 0.31. Fig. 3 shows the mass based size distributions of the fine particles as dispersed from the blends. The GSD of the dispersed micronized salbutamol was 2.8 whereas it was between 1.9 and 2.1 with the L-leucine coated fine powders.

The pure and coated salbutamol particles were stored in dry conditions i.e. over silica and at 43% relative humidity. Over 30 days the pure salbutamol particles were sintered forming amorphous bridges between adjacent particles. In contrast, all the coated particles did not change and remained intact and separate.

CONCLUSIONS

A novel method to simultaneously synthesize and coat pharmaceutical particles in the gas phase has been demonstrated. During the vapor deposition on the aerosol particles, L-leucine crystallized formed leafy-looking asperities pointing out of the surface of the particles. The resulting particles

Table I. Size Distributions of the Dispersed, Coated Fine Powders Delivered Without Lactose Carriers

Sample	Q (l/min)	FPF	MMAD (μm)	GSD
Salbutamol 30 g/l	15	0.39	1.95	1.58
L-leucine 1.0 g/l	60	0.46	1.65	1.68
Salbutamol 30 g/l	15	0.48	2.32	1.92
L-leucine 2.5 g/l	60	0.35	1.66	1.64
Salbutamol 30 g/l	15	0.39	2.42	1.78
L-leucine 7.5 g/l	60	0.47	1.71	1.61

The concentrations in the precursor solutions prior to particle preparation are given for each sample. Q, FPF, MMAD, and GSD are dispersing flow rate, fine particle fraction, mass medium aerodynamic diameter, and geometric standard deviation, respectively

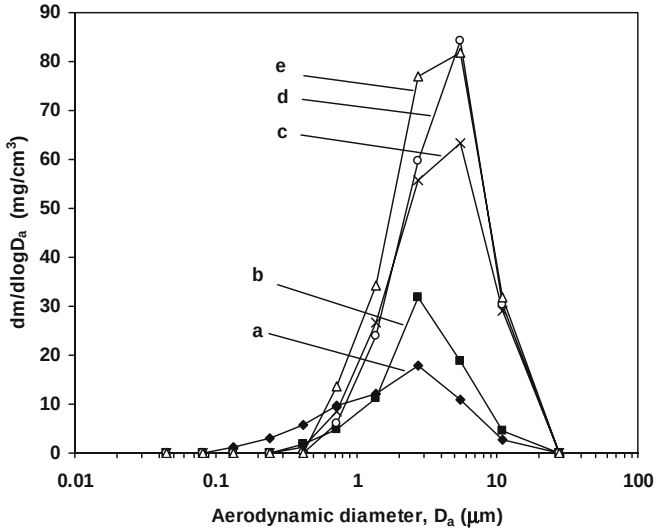

Fig. 3. Mass size distributions of the dispersed fine powders delivered with coarse lactose carriers. The dispersion flow rate was 60 l/min i.e. the dispersing jet Reynolds number 30700. Samples: **a** micronized salbutamol, **b** salbutamol 30 g/l and no L-leucine, **c** salbutamol 30 g/l and L-leucine 1.0 g/l, **d** salbutamol 30 g/l and L-leucine 2.5 g/l, and **e** salbutamol 30 g/l and L-leucine 7.5 g/l.

were spheres coated with a rough, crystalline L-leucine surface layer. The dispersion of the coated particles could be tested without lactose carriers due to their good flowability. With lactose carriers, the coated particles dispersed 3–5 times better than the commercial micronized salbutamol particles. Accordingly, the L-leucine crystals from a few up to hundreds of nanometers most probably reduced the contact area between the particle surfaces and this may have influenced the surface forces by reducing them. The crystallite size on the particle surface could be grown by increasing the amount of L-leucine vapor. Moreover, the L-leucine coating prevented sintering between adjacent particle surfaces when stored at moderate relative humidity. It is a continuous process where droplets are converted to ready-to-use dry powders in one step and in one reactor. Such well-flowable powders have high applicable potency in drug delivery systems, particularly, in the field of inhalation therapy.

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