

Use of additives in particle engineering of spray-dried nanosuspensions

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SUMMARY

Particle engineering via spray drying is a very useful tool for tuning particles' size, distribution, shape, density, and cohesiveness. Following this concept, dry powders for inhalation comprising large porous particles can be prepared. This is especially useful for pulmonary delivery, where particle size and density of a formulation play major role in delivery efficacy. However, to achieve large geometric size and low density, suitable spray drying additives have to be selected. Spray drying can be advantageously employed to formulate composite nanoparticles-containing microparticles. Embedding nanoparticles into microparticles preserves nanoparticles' benefits, such as improved bioavailability and dose uniformity, and allows their delivery into lungs.

In our work we prepared composite microparticles by spray drying of a drug nanosuspension at two atomising gas settings. Five additives (ammonium carbonate, albumin, glycine, leucine, or trileucine) were used during the spray drying in order to form porous/hollow particles. The effect of these additives on particle size and morphology, surface area, and aerodynamic behaviour was studied. At lower atomising gas setting, the fine particle fraction (FPF) for all excipients except trileucine ranged between 18.9 and 28.5%. Trileucine composite particles reached FPF of $53.0 \pm 2.7\%$; the mass median aerodynamic diameter (MMAD) was $2.0 \pm 0.2 \mu\text{m}$. Even better results were reached at higher atomising gas setting: all powders except for ammonium carbonate had FPF above 55%, trileucine having the highest FPF of $68.7 \pm 2.0\%$.

INTRODUCTION

Composite dry powders for inhalation present formulations that could replace the traditional, carrier-based formulations¹ as they eliminate concerns with homogeneity of drug distribution and aerosolisation, drug loading and particle size distribution. Another advantage of composite microparticles is the possibility to incorporate submicron structures, for instance drug nanoparticles, which offer enhanced dissolution rate, higher bioavailability, and better dose uniformity.²

Several techniques can be used to produce composite particles, for example supercritical fluid technology or solvent removing techniques such as spray or freeze drying. Spray drying is especially useful method since it is simple, controllable, one-step process that also allows production of porous/hollow particles. Such particles (i.e. particles with low density and large geometric diameter) can advantageously evade phagocytic alveolar clearance, which prolongs particles' action in the lungs, and improve powders' handling.³ Aside from spray drying settings, it is the excipients present in the feed that have impact on particle size and distribution, density, cohesiveness, and aerosolisation².

For successful production of porous/hollow particles, the particle engineering concept, which is based on the Péclet number, should be followed with the aim to create particles with high Péclet number.⁴ To achieve this, excipients with either low diffusion coefficient or low solubility should be used. So far, several substances were used in studies for production of such engineered particles.⁵ However, the particles in these studies were prepared by spray drying from a solution. Spray drying of a suspension demands a new investigation as the diffusion coefficients of the dissolved and suspended solutes differ dramatically.

The aim of this study was to investigate the influence of five additives with density-control potential (ammonium carbonate, albumin, glycine, leucine, and trileucine) on aerodynamic behaviour of spray dried nanosuspension. These additives have either low diffusion coefficient, low solubility in water, or can act as pore forming agents. Moreover, the particle size, morphology, and surface area were characterised.

MATERIALS AND METHODS

Preparation of the nanosuspension

The nanosuspension was produced by wet media milling of budesonide (5% (w/v)) in a DYNO[®]-MILL Multi Lab (WAB, Switzerland). Based on previous studies, the suspension was stabilised using D- α -tocopherol polyethylene glycol 1000 succinate (TPGS) in ratio 1:4 to the drug amount. The shaft speed was 12 m/s and the filling ratio of the milling medium (SiLibeads type ZY Premium, Sigmund Lindner, Germany) was 60%.

Spray drying of the nanosuspension

We spray dried the nanosuspension to tune the particles' aerodynamic properties and to increase the nanosuspension's stability. For the spray drying process, we used Büchi Mini Spray Dryer B-290 coupled with Dehumidifier B-296 and molecular sieve (all Büchi Labortechnik, Switzerland). The inlet temperature, the feed flow rate, and the aspirator flow rate were set to 200°C, 9 mL/min, and 35 m³/h, respectively. The atomising gas was set by a rotameter to either 30 or 50 mm (corresponding to 7.3 or 22.9 L/min, respectively). The total concentration of the feed was 1% (w/v). Budesonide's relative concentration was 50% of the solids. The other 50% was filled by one of the additives: ammonium carbonate, albumin, glycine, leucine (the particles are hereafter referred to as AC, Alb, Gly, Leu; all Sigma-Aldrich AG, Switzerland), or trileucine (hereafter referred to as TriLeu; Bachem AG, Switzerland).

Next Generation Impactor (NGI)

The Next Generation Impactor (Copley, United Kingdom) was used to determine the aerodynamic diameter of the spray-dried powders. For each measurement, Vcaps capsule (size 3; kindly donated by CAPSUGEL[®], France) and the powder were conditioned at 30 °C and relative humidity of 43% (\pm 2%) for one week. For each sample, a capsule containing approximately 5 mg of the powder was prepared. The capsule was placed in a monodose dry powder inhaler (type RS01 Mod. 8, kindly donated by *Plastiapre S.p.a., Italy*) and the powder was lead through the impactor at airflow of 100 L/min for 2.4 s. Prior to each measurement, the collection cups were coated with a 1% (w/v) glycerol in ethanol solution. The deposited powders were recovered by ethanol extraction and each of these ethanolic solutions was quantified using an HPLC[®] (Agilent Technologies, USA, with HyperClone ODS column (150 x 4.6 mm, 5 μ m, Phenomenex[®])) The FPF was calculated as the fraction of particles with an aerodynamic diameter < 5 μ m.

Scanning electron microscopy (SEM)

SEM was used to examine the particle size and morphology of the spray-dried samples. The samples were first coated with gold for 45 seconds using a ThermoVG Scientific Polaron Sputter Coater. A Supra 40VP microscope (Carl Zeiss, Germany) was used to take the images. The InLens detector was used, with the working distance of 5 mm and accelerating voltage of 5 kV.

Surface area measurement (BET)

Before the measurement, the samples were purged overnight with nitrogen using a FlowPrep 060 Sample Degas System (Micromeritics, Germany) to remove any moisture. A Gemini V analyser (Micromeritics GmbH, Germany) was used to measure the surface area of the samples with nitrogen as the adsorbent. Nine points (P/P₀ 0.05-0.25) were measured to calculate the surface area.

RESULTS AND DISCUSSION

Preparation of the nanosuspension

Figure 1 (left) shows the development of the particle size during nanomilling. The particle size was reduced rather quickly after the start of the milling process. The final particle size of the nanomilled active substance was 258 \pm 17 nm and it was achieved at specific energy input of around 170 MJ/kg (blue line), which corresponded to milling time of 150 min. After the milling, a small sample of nanosuspension was freeze dried to obtain a sample for SEM characterisation. Figure 1 (right) shows the SEM image of freeze dried budesonide nanosuspension. Nanoscale crystals were apparent throughout the sample.

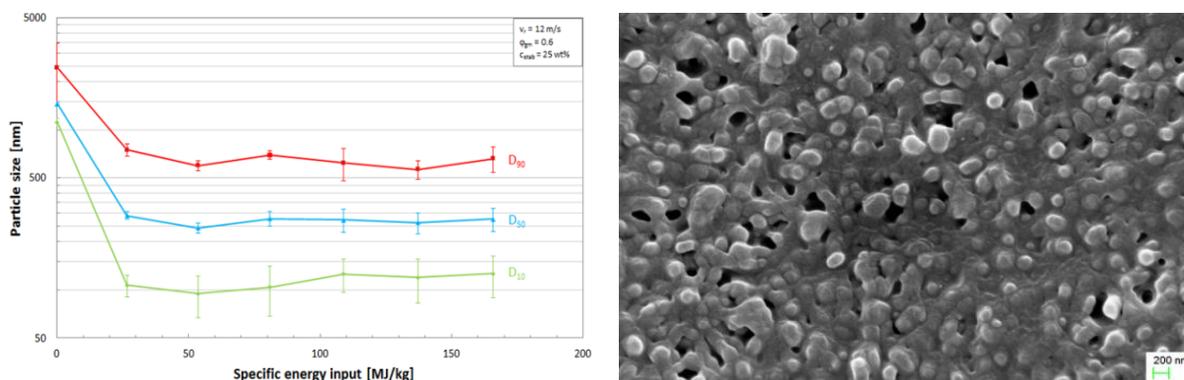


Figure 1 – Left: Development of particle size reduction during nanomilling. Right: Freeze-dried nanosuspension after nanomilling. Error bars represent SD, n=3.

Spray drying and characterisation

1) Spray drying at low atomising gas

The powders obtained at atomising gas set to 30 mm showed various morphologies (Fig. 2). Particles with AC, Alb and Gly were crumpled, although each to different extent. Especially Alb particles showed almost collapsed morphology. Surprisingly, AC particles did not show any kind of pores that were expected to form by decomposition of ammonium carbonate and evaporation of the decomposition products. Leu particles, on the other hand, formed porous shells with a sponge-like inner structure. Particles sprayed with TriLeu collapsed and formed folded shells.

Geometric median particle size (d_g) of powders sprayed at 30 mm setting with Alb, Gly, and Leu was between 7.3 and 7.9 μm . With AC the size was smaller ($5.80 \pm 0.02 \mu\text{m}$) due to lower solids concentration in the spray drying feed. TriLeu had the lowest d_g of $3.5 \pm 0.1 \mu\text{m}$.

Surface area analysis showed that the crumpled particles reached similar values in range from $2.0 \pm 0.4 \text{ m}^2/\text{g}$ (Gly) to $5.9 \pm 2.2 \text{ m}^2/\text{g}$ (AC). Expectably, Leu had larger surface area of $16.6 \pm 0.4 \text{ m}^2/\text{g}$. Surface area of TriLeu particles was just slightly lower ($16.2 \pm 0.4 \text{ m}^2/\text{g}$).

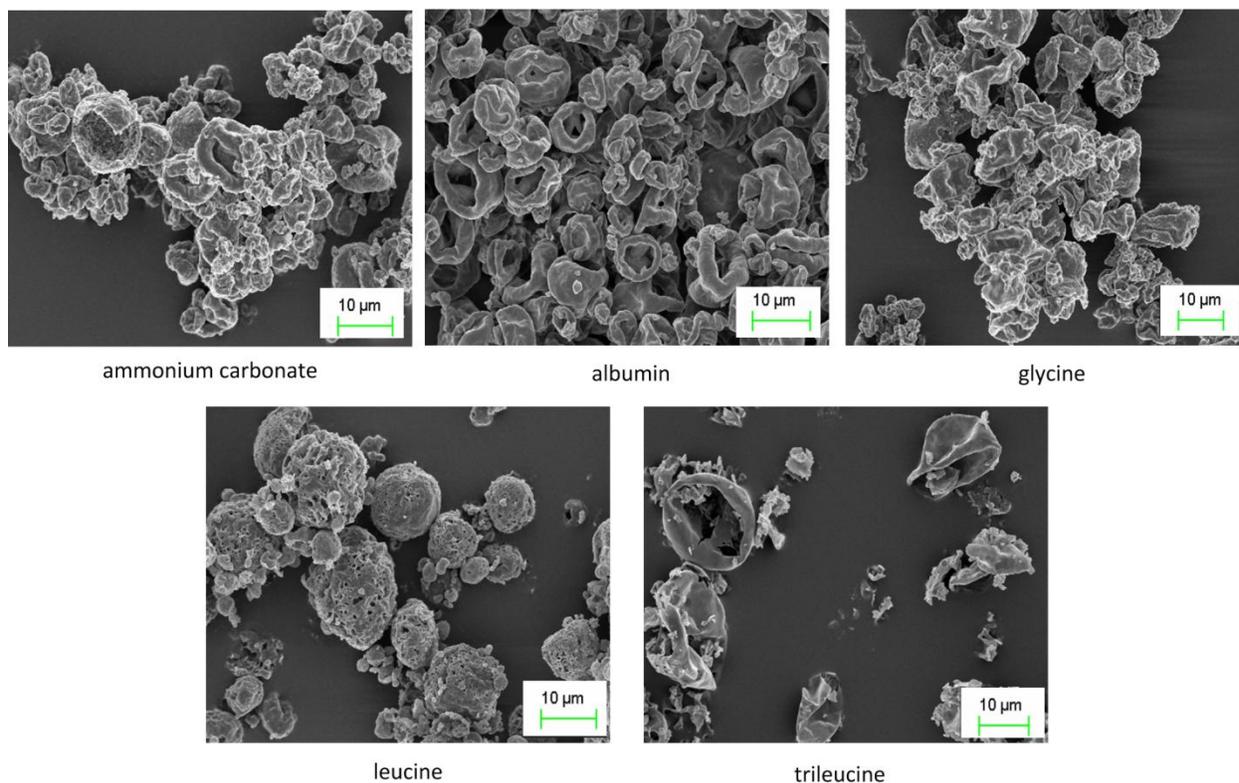


Figure 2 –Powders of nanosuspension spray dried with different additives at atomising gas setting 30 mm.

2) Spray drying at high atomising gas

At high spray gas setting (50 mm), the median geometric size of all powders ranged between 2.1 and 2.5 μm . The morphologies of the powders showed smaller differences among each other. AC and Gly particles formed smooth spheres, while Gly particles were slightly crumpled. Leu particles exhibited both smooth and porous surfaces. Particles formed with TriLeu as additive appeared to be less collapsed than those formed at low atomising gas setting.

Except for AC, the surface area of the samples increased. Alb and Gly particles reached significantly higher values $6.75 \pm 0.29 \text{ m}^2/\text{g}$ and $3.89 \pm 0.09 \text{ m}^2/\text{g}$, respectively. Also TriLeu particles' surface area increased significantly to $25.11 \pm 1.78 \text{ m}^2/\text{g}$, while Leu particles increased only a little to $17.12 \pm 0.14 \text{ m}^2/\text{g}$. The statistical evaluation was done by Student's t-test.

Aerodynamic behaviour

Despite the porous morphology and the large surface area of Leu, which would suggest particles of low density, the FPF of these particles reached only $28.5 \pm 2.1\%$ (Fig. 3, left). The highest FPF was achieved by TriLeu, which reached $53.0 \pm 2.7\%$. Better performance of TriLeu was probably given by the smaller MMAD (Fig. 3, left, blue diamonds), caused likely by smaller geometric particle size (Fig. 3, left, red triangles) on the one hand and thin folded shells on the other hand.

Irrespective of the additive present in the powder after spray drying, the FPF (Fig. 3, right) increased above 55% in almost all powders sprayed at 50 mm atomising gas setting. Although Alb, Leu, and TriLeu particles had similar morphology as at low atomising gas setting, the difference between their FPF vanished as they all reached similar d_g values.

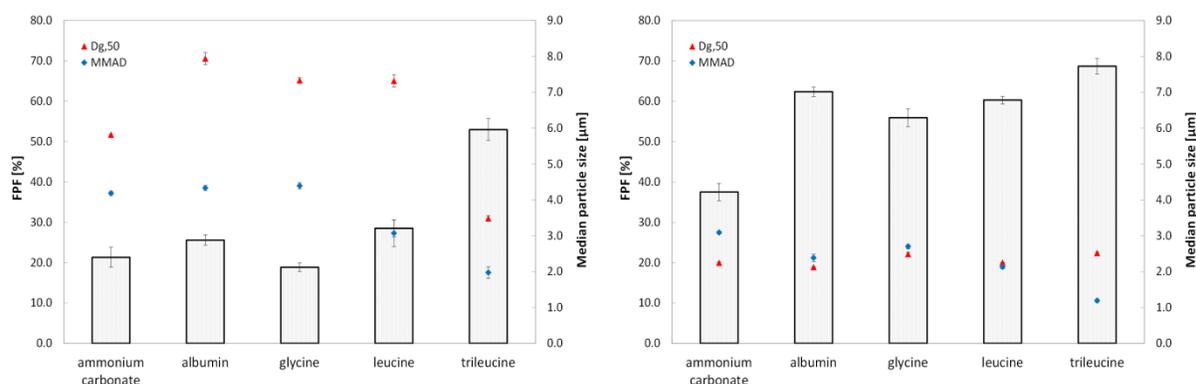


Figure 3 – Left: Fine particle fraction, MMAD (blue diamonds) and median particle size (Dg,50; red triangles) of powders of nanosuspension spray dried with different additives at atomising gas setting 30 mm. Right: Fine particle fraction, MMAD (blue diamonds) and median particle size (Dg,50; red triangles) of powders of nanosuspension spray dried with different additives at atomising gas setting 50 mm. Error bars represent SD, n=3.

CONCLUSION

In our study, we investigated the influence of five additives, namely ammonium carbonate, albumin, glycine, leucine, and trileucine, on properties of spray-dried nanosuspension. Under the same spray drying conditions, the particle size, surface area, morphology, as well as fine particle fraction of the powders varied with the additive used. Despite expectation, ammonium carbonate did not form porous particles and aerodynamically performed worst even at high spray gas setting. Irrespective of the spray gas setting, trileucine seemed to be the best additive in terms of FPF and surface area. However, if one would take into account also price of the substances, use of other additives, such as albumin or leucine, or their combination, together with optimisation of spray drying conditions would seem as better choice. Future work will study the effect of different particle morphology on dissolution of the microparticles and redispersibility of the nanoparticles.

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