Manufacturing of Taylor Made Carrier Particles for Inhalation Therapy by Spray Drying

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Abstract

Mannitol, a sugar alcohol frequently used as a matrix material in pharmaceuticals, allows for tailoring the surface morphology when applied as carrier particles by variation of the drying air temperature as already confirmed in a small lab dryer [1] producing carrier particles d < 20 µm. It was found that high drying air temperature leads to rough surfaces, structured by larger crystals, and fairly smooth particles are formed at low drying air temperatures. It is expected for the active species to adhere stronger to rough surfaces compared to smooth surfaces. New experiments were performed spraying 15 % by weight mannitol with a multiple hole rotary atomizer in combination with a larger drying tower. The atomizer with D = 100 mm diameter is equipped with 50 inclined bores operating within the laminar open channel flow range. The atomizer is able to generate highly uniform sprays with low span values SP = (dv.90-dv.10)/dv.50 < 1 [2]. Only narrow PSD sprays can be expected to lead to a uniform high quality carrier system. The target particle size was 62 µm achieved at 7200 rpm. The morphology of particles was altered by changing the air inlet temperature of the dryer leading to air outlet temperatures within the range of 80 °C to 130 °C. The particles as obtained from the mannitol solution are characterized by different analytical methods relevant for their pharmaceutical application. Details on the PSD are reported.

Introduction

The key features of any dry powder inhalate are uniformity of dosing and the generation of a reproducibly high fraction of the active reaching the deep lung. The latter is achieved by using powders with aerodynamic diameters between 1 µm and 5 µm. However, the reproducible dispense of the dose (e.g. volumetric dosing in multiple dose inhaler) requires powders of good flowability, which is typically not the case for particles of this size. The solution to this problem is the attachment of the drug particles (1 µm – 5 µm) to a carrier consisting of larger particles (50 µm – 100 µm), that exhibit sufficient flowability. An important issue of such drug-carrier-formulations is the detachment of the active fines from the carrier upon inhalation in order to ensure deep lung deposition without impaction on the upper respiratory tract walls. Particle interactions between the active and the carrier play the decisive role for this mechanism.

Subject of literature is the modification of the particle interaction between active and carrier. The modification of the carrier surface morphology has proven to be an effective tool to reach this goal even though adhesive forces are also dependent on other geometric factors like particle size, shape and morphology as well as on physical and chemical properties of the interacting partners. In spite of the predominant use of α-lactose monohydrate which is contained in the majority of commercially available powder inhalers, α-lactose monohydrate has several properties that are disadvantageous for the use as carrier substance. Besides low yield due to pronounced stickiness at the tower walls, the most important drawback is its transformation into the amorphous state by spray drying which makes the substance unsuited for this particle generation process due to the risk of instability during storage. However, spray drying is a dedicated technology in the production of carrier particles for inhalation therapy, because spray dried products are typically of spherical shape [3]. In contrast to crystals besides their sharp edges and corners leading to abrasion upon impact, due to their different crystal surfaces exhibit different affinity to the active, spherical particles have a much more homogeneous surface in terms of affinity to adhering active substance particles. This is the reason why active substances can not be detached from crystal sites of high affinity to the active resulting in poor lung deposition.

In comparison to α-lactose monohydrate, mannitol lacks this drawback. Even though mannitol is considered as alternative for α-lactose monohydrate in the literature (Adi et al. 2007 [5], Harjunen et al. 2003 [6], Saint-Lorant et al. 2007 [7], Steckel et al. 2004 [8], Tee et al. 2000 [9]), there is no study analyzing the surface topography of spray dried mannitol in dependence of the spray drying parameters systematically, although the surface topography is of

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high importance for the particle-particle interaction between active substance and carrier. Furthermore the possibility of specific manipulation of the surface topography of mannitol is not yet discussed in the literature.

The present study focuses on the modification of the surface topography of mannitol by spray drying. Preliminary experiments were performed with a small pilot dryer producing particles d < 20 µm with a high speed commercial rotary atomizer, i.e. with a wheel diameter D = 50 mm. In an attempt to increase particle size and to narrow particle size distribution, further studies were carried out using a rotary atomizer with D = 100 mm diameter in a larger tower. The atomizer is equipped with 50 inclined bores operating within the laminar open channel flow range. The atomizer is able to generate sprays with low span values SP = (dv.90-dv.10)/dv.50 < 1, [2], ensuring uniform transport, drying and solidification processes in the drying tower and finally leading to equal or close to equal surface characteristics of individual spray dried particles.

Particle surface and particle formation were examined by means of SEM as obtained from the small and larger pilot plant in addition to the measurement of particle size, density and uniformity of dosage. The influence of the product surface topographies on the in vitro drug delivery to the lungs was investigated using an impactor.

Materials and Methods

Comminution of the active material

Salbutamol sulphate representing the active substance used in this study was micronized using the air jet mill 50 AS (Hosokawa Alpine, D-Augsburg). The injection pressure was set to 6 bar, milling pressure to 2 bar and the feeding rate was adjusted to 1 g/min. The obtained material, hitherto nominated as "fines", exhibits a mean particle diameter of 1.80 µm (x10 = 0.65 µm; x50 = 1.80 µm; x90 = 4.89 µm).

Spray drying of mannitol

Pilot I: Preliminary experiments were carried out using a small pilot (I) dryer (Niro Atomizer, Niro, DK-Copenhagen) with a rotary atomizer. Aqueous mannitol solutions, 15 % b. wt. were dried with a feed rate of 14 ml/min and the rotational speed of 27500 rpm (4 bar air pressure at turbine) of the wheel with 50 mm diameter containing 24 channels. Tower dimensions: diameter 800 mm, total height 1500 mm. The outlet air temperature was varied between 60 °C and 120 °C.

Pilot II: larger particles were produced in Pilot II with a 100 mm wheel containing 50 3 mm bores running at a speed of 7200 rpm. The wheel is also shown later in **Figure 3**. The feed rate of the 15 % b. wt. aqueous mannitol solution was dried with a feed rate of 180 ml/min. The tower dimensions were: diameter 3700mm, total height 3700 mm. The outlet temperature was varied within 80 to 130 °C.

Mannitol (Pearlitol SD 200) was provided by Roquette, F-Lestrem. Salbutamol sulphate was received from Lindopharm, D-Hilden.

Preparation of drug-carrier-mixtures

8 g batches of ordered mixtures were prepared with the spray dried particles generated by the small lab dryer (Niro Atomizer, Niro, DK-Copenhagen) using a carrier to drug ratio of 99:1. Half of the carrier material was weighed into a stainless steel vessel, then salbutamol sulphate was added and finally, the second half of the carrier material. The powder was mixed in a Turbula® mixer (T2C, Bachofen AG, CH-Muttenz) at 65 rpm for 90 min and allowed to settle for 2 h before further treatment.

Particle size measurements

Laser light diffraction (Helos/KF-Magic, Sympatec, D-Clausthal-Zellerfeld) including a dry dispersing system (Rodos, Sympatec, D-Clausthal-Zellerfeld) was used to determine the particle size distribution of the spray dried mannitol particles. The measurements were carried out at the air injection pressure of 2.6 bar and the negative suction pressure of 70 mbar.

Particle surface investigations

The powder samples were examined using a Hitachi H-S4500 FEG scanning electron microscope (SEM) operating at 1kV.

Uniformity of dosing

Uniformity of dosing was checked on spray dried mannitol particles obtained using the small lab dryer (Niro Atomizer, Niro, DK-Copenhagen). The powder was filled into the cartridge of the Novolizer® dry powder inhaler (Viatris, D-Bad Homburg). 50 doses were discharged from the inhaler and the mass of each dose was recorded.

Assessment of the fine particle fraction

The aerodynamic assessment of fine particle release was performed using the next generation impactor (NGI) (Copley Scientific, UK-Nottingham). The small cups of the NGI were coated with 2 ml coating agent (solution of 5% of a mixture of glycerol and polyoxyethylene-20-cetylether (95:5) in isopropanol), the large cups with 4 ml. The pre-separator was filled with 10 ml diluted acetic acid. The measurements were performed using 79.3 l/min flow rate and 3 s calculated opening time. The flow rate was measured with a digital flowmeter (Model DFM, Copley Scientific, UK-Nottingham). Pumps (Type SHC P3, Type HC P3) and the critical flow controller (Model TPK) were also from Copley Scientific. The ordered mixture was filled in the powder container of a Novolizer® (Viatris, D-Bad Homburg) which was fixed to the throat of the impactor by a suitable adapter. The dose of active ingredient on the stages was determined by HPLC. The fine particle dose is calculated as the dose of active ingredient exhibiting an aerodynamic diameter of < 5µm. The fine particle fraction (FPF) is defined as the fine particle dose divided by the whole dose of active found in the impactor.

Statistical methods

The statistical analysis of the experimental data was carried out using the two-sample two-tailed t-test. In cases, where the preliminary F-test for the variances indicated that the variances of two batches were significantly different, a two-sample t-test was performed assuming unequal variances. Probability (*p-value) was < 0.05.

Results and Discussion

Mannitol first was spray dried in Pilot I at 60 °C, 90 °C and 120 °C outlet air temperature using the small lab dryer (Niro Atomizer, Niro, DK-Copenhagen with a 50mm diameter wheel) and at 140 °C and 180°C outlet temperature using the rotary atomizer with D = 100mm diameter. In order to estimate particle surface and morphology of the individual products, SEM micrographs were taken. In addition, particle size was determined. Possible changes in flowability were assessed by uniformity of dosing tests on samples spray dried using the small lab dryer (Niro Atomizer, Niro, DK-Copenhagen). On these samples, the influence on drug delivery to the lungs was also checked by the aerodynamic assessment of fine particles.

Particle surface

The results of the SEM investigations on the surface of mannitol spray dried using the small lab dryer (Pilot I) are presented in **Figure 1**. The increase of the outlet air temperature enhances roughness of the particle surface and induces the formation of distinct holes in the wall of the particles. The hole represents the area where excess solvent leaves the particle already surrounded by a crystallized mannitol layer. According to Vehring 2008 [4], generally the size of the droplet decreases until the concentration of the solute exceeds saturation and crystallization takes place at the particle surface. At a high spray drying temperature super-saturation at the surface of the droplet occurs at an early stage of the drying process leading to crystallization and formation of an outer shell, through which a hole is formed in order to release excess solvent, which is still present in the inner of the droplet. Spray drying at lower temperatures allows for a slow evaporation during the spray drying process, allowing the droplet to become smaller before super-saturation is reached and the outer shell is formed. Thus, there is less solvent left in the inner of the droplet, probably preventing the emergence of a hole. Furthermore, the product spray dried at 120 °C shows larger crystals, than the product spray dried at 60 °C. This is somewhat unexpected, as with high drying temperature the time for crystal growth is shorter compared to a low drying temperature.

In order to explain this phenomenon, the crystallization behavior of the droplets of a mannitol solution has been studied using a hot stage microscope. The mannitol solution droplet was dried on a hot stage at 60 °C and 120 °C. At 60 °C, the micrograph shows several fine needles, whereas the droplet, which has been dried at 120 °C exhibits only one crystal nucleus that has grown in all directions.

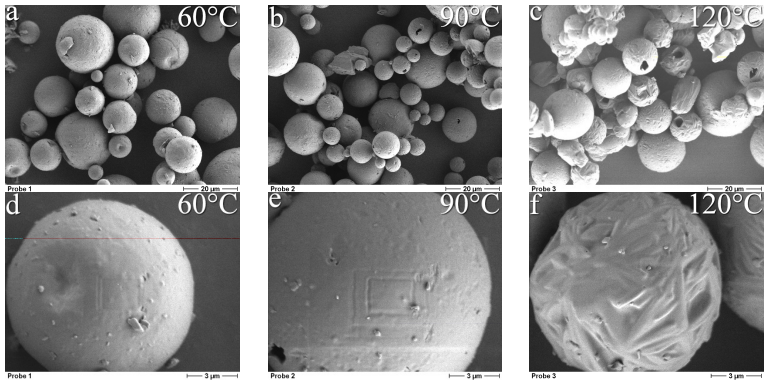

Figure 1. SEM micrographs of spray dried mannitol from Pilot I, feed temperature 40 °C, feed concentration 15%, outlet air temperature 60 °C (a and d), outlet air temperature 90 °C (b and e), outlet air temperature 120 °C (c and f)

With samples subjected to 60 °C the gradual evaporation of the solvent takes place followed by crystal nucleation. Due to the high amount of crystal nuclei, crystal growth is limited by the boundaries of adjacent crystals. In contrast, at 120 °C, the droplet looses water quickly. The viscosity of the mannitol solution increases. However there are no multiple crystal nuclei visible. Only one crystal nucleus is formed within the highly concentrated solution or even water free melt. This nucleus is growing in all directions. So actually, dependent on the drying temperature, two different crystallization processes take place resulting in different particle surface topographies.

Particle sizes from Pilot I

The particle sizes of mannitol spray dried at 60 °C (mannitol A) and 120 °C (mannitol B) using the small lab dryer were determined by laser diffraction, as shown in **Figure 2**. The particle size of mannitol spray dried at 120 °C is larger (x10 = 4.96 µm; x50 = 13.64; x90 = 23.87 µm) compared to mannitol spray dried at 60 °C (x10 = 3.02 µm; x50 = 10.11; x90 = 18.95 µm). Given the similar drop size leaving the rotary atomizer of the spray dryer, it is striking, that the spray dried particles obtained at 120 °C are larger than particles obtained at 60 °C. According to Walton 2000 [3] and Vehring 2008 [4], the size of the droplet decreases upon drying until the concentration of the solute exceeds saturation and crystallization takes place at the particle surface. At a high spray drying temperature the evaporation of the solvent proceeds faster and super-saturation followed by the formation of an outer shell takes place at an earlier stage of the drying process in comparison to low spray drying temperatures. Thus particles dried at 120 °C are of a larger size than the ones dried at 60 °C, thus exhibiting a porous or hollow structure.

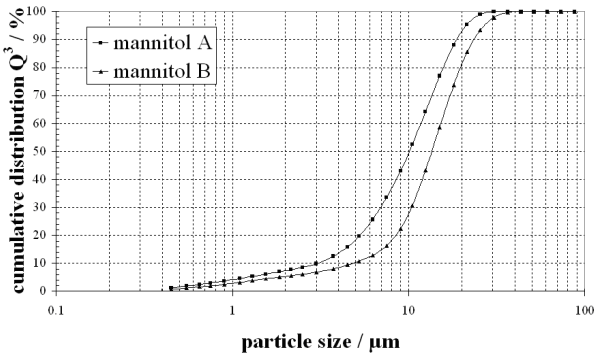

Figure 2. Laser diffractogramm of mannitol spray dried at 60 °C (mannitol A) and 120 °C (mannitol B) using the small lab dryer, i.e. Pilot I, (Niro Atomizer, Niro, DK-Copenhagen), cumulative volume distribution
Uniformity of dosing

The dosage uniformity of mannitol particles spray dried at 60 °C (mannitol A) and 120 °C (mannitol B) using the small lab dryer was tested by discharging 50 doses from the Novolizer® inhaler; data are listed in **Table 1**. The mean of the mass delivered and the high standard deviation of mannitol spray dried at 60 °C indicate poor flowability, which is in contrast to the measurements carried out with mannitol spray dried at 120 °C. Probably increasing surface roughness decreases the inter-particle contact area and enhances dosing due to increased flowability. Another factor improving the dosing behavior is particle size. A second indicator of improved flowability is the significantly higher mass of the doses in case of mannitol spray dried at 120 °C. Hence the higher roughness or groove depth within the surface of mannitol particles spray dried at 120 °C result in improved uniformity of dosing.

Table 1. Line 1 and 2 average mass and standard deviation of 50 doses each taken from 3 mixed charges per sprayed product and dispersed by a Novolizer® inhaler. Line 3 and 4: fine particle fraction (FPF) of these samples and corresponding standard deviation

	mannitol A	**mannitol B**
average / mg	7.10	9.96
standard deviation / mg	±1.58	±0.82
fine particle fraction (FPF)	0.71	0.52
standard deviation (FPF)	±0.05	±0.03

Fine particle fraction (FPF)

Line 3 and 4 in **Table 1** displays the results of the assessment regarding fine particles. The FPF of ordered mixtures consisting of salbutamol sulphate and mannitol spray dried at 60 °C (mannitol A) outlet temperature or 120 °C (mannitol B) using the small lab dryer were determined. The FPF of mixtures containing mannitol spray dried at 60 °C is higher than the one of mixtures containing mannitol spray dried at 120 °C. The FPF is dependent on the adhesion forces between active ingredient and carrier. The outcome of this experiment shows that the smooth surface of mannitol spray dried at 60 °C outlet temperature leads to a significantly higher FPF than the rough surface of mannitol spray dried at 120 °C outlet temperature. Obviously the rougher surface provides a greater contact area for the active, leading to the increase of interactive forces and deterioration of the detachment from the carrier particle. This may be responsible for the decrease of the fine particle fraction of mannitol spray dried at 120 °C compared to mannitol spray dried at 60 °C. Another effect of the rough surface might be shelter against the drag forces exerted by the air flow during inhalation.

Carrier particles from Pilot II

Due to the flow conditions in the wheel according to **Figure 3**, laminar threads are formed at the outlet of each bore. The drop or particle size scales with the capillary length L_c. Considering the centrifugal acceleration $a = R\omega^2$ at the circumference of the atomizer, the surface tension of σ = 68 mN/m and the density of the solution ρ = 1030 kg/m^3 we obtain $L_c = (\sigma/\rho a)^{1/2}$ = 48 µm. The specific non-dimensional flow rate per bore is $V^* = V(a^3\rho^5/\sigma^5)^{1/4}$ = 20 corresponding to an estimated drop size of 93 µm from $d = L_c \cdot V^{*0.22}$. For explanation of the characteristic numbers and drop mean diameter estimates see also [2]. Offline measurements of the spray with a MALVERN LDS indicated 6 % larger drop sizes with $d_{v.50}$ = 99 µm as a mean droplet size. Assuming nonporous particles, solution droplets would shrink to about d = 40 µm. The actual mean particle size is 62 µm as shown in **Figure 4** suggesting a porosity/void core of about 50 %, - a very common value in spray drying. The particles are formed out of droplets coming from Rayleigh breakup of laminar threads. The PSD span $SP = (d_{v90}-d_{v10})/d_{v50}$ = 0.75 is very small compared to the particles from Pilot I (with SP = 1.5). The particles show reasonably equal morphologies.

The basic behavior of topology formation during solidification takes place in a similar way on particles dried in Pilot II despite of the larger particle size. Particles dried at low temperature give rise to a smooth surface and particles dried at higher temperatures lead to rough surfaces, see **Figure 5**. It is expected, the larger particle compared to those from Pilot I, will provide an even more uniform dosing behavior. By tailoring the surface topology simply by proper air temperature control it is expected to provide a large enough contact area for the fines to adhere. Characterization of particles from Pilot II regarding pharmaceutical and physical properties is ongoing.

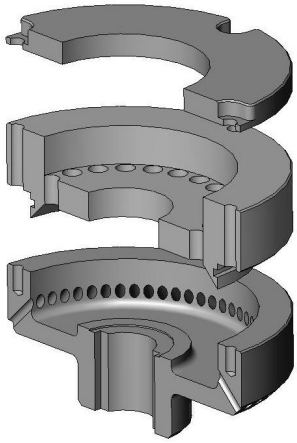

Figure 3. Explosion drawing of laminar operated Rotary atomizer in Pilot II containing 50 holes

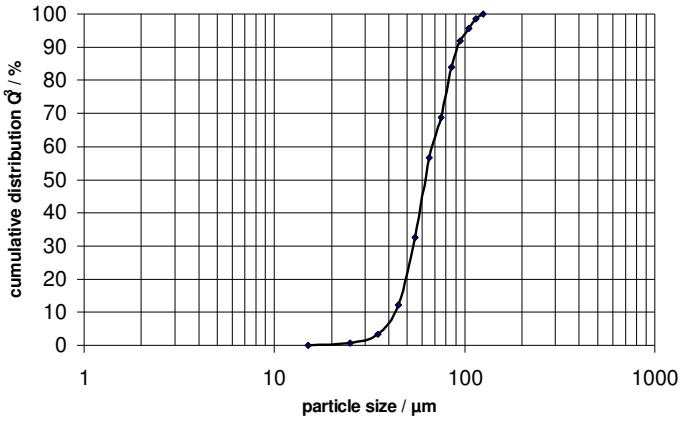

Figure 4. PSD from laminar operated rotary atomizer

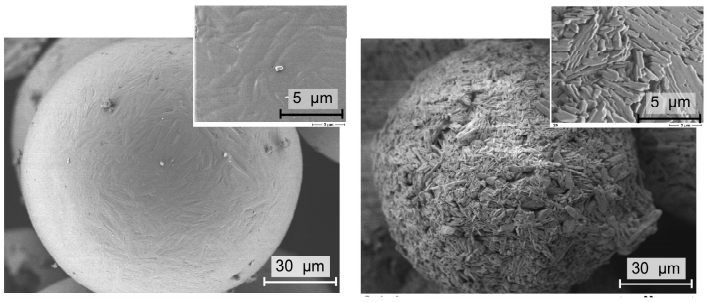

Figure 5. SEM of spray dried mannitol particles from pilot II. The particles in the left picture were obtained at outlet temperatures of 80°C. The particles in the left picture are formed at drier outlet temperatures of 130°C. The close-up in the pictures gives an impression of the surface topology.

Conclusion

This study demonstrates that combining the effect of drying temperature control as well as particle size control allows for adjustment of spray dried mannitol particles as well suited carrier particles for inhalation processes. Particle size control is achieved by a laminar operated atomizer LAMROT. The surface properties of the dried particles can be adjusted by changing the drying air temperature. High temperatures lead to rough surfaces of mannitol increasing both the particle size and roughness. Hence the performance of inhalates can be tailored and optimized.

Acknowledgements

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