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Research paper

Influence of mechanical activation on the physical stability of salbutamol sulphate

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Abstract

In order to obtain the optimal particle size distribution for pharmaceutical powders in dry powder inhalers the particles have to be micronised. In most cases the process of micronisation is connected with a high input of energy which induces disorder and defects on the surface of the drug particles and as a result changes in the crystallinity. Consequently, changes in the physical stability of the powders may occur. To investigate changes on the physical stability of the powder, different analytical methods are used in the present investigation: laser diffraction, Differential Scanning Calorimetry (DSC), isothermal microcalorimetry and DVS-method.

Air-jet-milling is one of the most frequently used techniques in the pharmaceutical industry, in order to obtain particles of respirable size. In the treatise described here the influence of the critical parameters of the process, i.e. feed pressure, grind pressure and feed rate is assessed for salbutamol sulphate. The grind pressure is of utmost importance with respect to particle size distribution and the physical powder stability. For salbutamol sulphate, ground with a MC Jetmill 50, a grind pressure of 6 bar has been found optimal. Pressures below 6 bar are not sufficient to produce the required reduction in particle size. The feed pressure and rate have negligible influence on the powder quality. Furthermore, the micronisation process is optimised to achieve respirable particles while minimising the amorphous content. A correlation between mechanical activation and the amount of the amorphous regions is showed clearly.

Air-jet-milling has been compared to ball milling in this investigation. In pilot tests ball milling was not suitable to achieve the needed particle size distribution, however, it generates a specific quantity of amorphous material. With the help of specific amorphous regions in the powder, the sensitivity of the used methods for salbutamol sulphate can be examined.

Keywords: Micronisation; Salbutamol sulphate; Particle size; Amorphous; Mechanical activation

1. Introduction

Salbutamol sulphate is a β_2-sympathomimetic agent used in the treatment of asthma and chronic obstructive pulmonary diseases in form of metered dose inhalers and dry powder inhalers.

In order to guarantee full effectiveness, an optimal particle size distribution is of an utmost importance. Zanen et al. [1] investigated the optimal particle size of salbutamol for application in mild asthmatics. It was found, that the optimal effective particle size is 2.8 μm in diameter.

In order to meet these requirements, the raw material must be subjected to a micronisation process. In the studies described here, micronisation was carried out using a spiral air-jet-mill.

Spiral air-jet-mills produce size reduction through particle impact and attrition and are capable of producing super- to ultrafine particles (1–15 μm) within a very narrow size range [2–5]. The material to be ground and the feed gas (in this case nitrogen) are introduced into the flat, circular grinding chamber using a Venturi-system (Fig. 1).

The amount of energy required to effect fracture depends on the hardness and particle size of the material and the type of stress applied. According to fracture theory, the hardness of a material increases as its particle size decreases. Consequently, milling of finer materials requires more energy and therefore higher impact speeds than coarse

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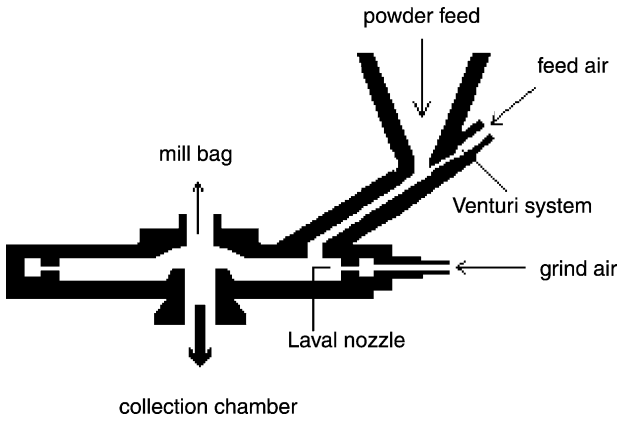

Fig. 1. Schematic diagram of a spiral jet mill.

milling. In addition, when fine particles are being milled, impact speeds are likely to be much lower as a result of air friction, and interparticulate collisions are likely to occur more frequently [6,19].

The concentration of the product affects both the cut point and the separation efficiency of the classifier. If the concentration is too high, separation efficiency deteriorates and coarse particles are separated along with fine particles [7].

In the studies described here, a type of mill was used which has an outlet on the bottom of the grinding chamber. Two end product fractions are of interest (Fig. 1):

- the fraction collected in the container beneath the grinding chamber (this accounts for the majority of the end product);
- the superfine particles collected in the mill bag of the cyclone system (these account for 15–20% of the end product).

In order to avoid the fine particles being lost, the two fractions have to be combined. The disadvantages of this type of mill are that it produces a slightly lower yield and a less homogeneous product.

The degree of comminution obtained depends on the critical milling parameters. The most important parameters are feed rate, feed pressure and grind pressure. Each of these parameters was varied in experimental studies to obtain an optimum particle size distribution at low levels of material stress. The particle size distribution was assessed by laser diffraction and SEM.

Depending on the level of energy input, milling can give rise to disorder, defects or even amorphous regions on the surfaces of the crystals. Even very small quantities of amorphous material can have a marked effect on the physical and chemical stability of the product. Amorphous material is thermodynamically unstable. Upon water absorption and depending on temperature, amorphous material is preferentially converted to thermodynamically stable crystalline material. This process frequently coincides with particle growth [8].

Amorphous material in a solid can also be produced mechanically using a centrifugal ball mill. This enables a correlation to be drawn with physically produced amorphous material and allows the sensitivity of analytical methods to be evaluated.

To investigate changes on the physical stability of the micronised powder DSC, isothermal microcalorimetry and DVS-method are used. This methods have already been described in numerous publications. Above all, lactose as a case substance was investigated [9–18]. Ward and Schulz used DSC, TG (Thermo Gravimetry), XRPD (X-Ray Powder Diffractometry) and DVS-method for the investigation of salbutamol sulphate and likewise analysed a micronised product but without taken the amount of mechanical activation into account [8].

The aims of the present study are to evaluate the critical parameters of micronisation with an air-jet-mill, optimise this process with respect to minimising the amorphous content while simultaneously achieving respirable particles. In addition, a possible correlation between mechanical activation and the amount of the amorphous regions in the product should be tested.

2. Materials and methods

2.1. Materials

Salbutamol sulphate (batches Nos. 200713, 200921, 1001825) was supplied by Boehringer Ingelheim Pharma KG (Ingelheim, Germany).

2.2. Methods

2.2.1. Ball milling

Samples (10 g) of batch No. 200713 were prepared by ball milling in a 250 ml agate mortar with four agate balls (diameter 20 mm). The grinding time in the ball mill (Type S1, Retsch, Haan, Germany) was varied from 5 min to 5 h.

The samples were stored over phosphorous pentoxide to protect them from moisture.

2.2.2. Air jet milling

Micronised powders were prepared with a MC Jetmill 50 (Jetpharma, Balerna, Switzerland). Nitrogen was used as feed gas. Extant room conditions came to 21 ± 1°C and 45 ± 2% RH. The milled samples were stored over phosphorus pentoxide.

2.2.3. Particle size analysis

The particle size distributions of salbutamol sulphate were measured using powder laser diffraction, HELIOS-SYSTEM (Sympatec, Clausthal-Zellerfeld, Germany). Samples were introduced through the RODOS dry powder

feeder. The supply pressure of the injector was at 3 bar. The optical concentration reached values between 4 and 8%.

2.2.4. Particle morphology

The morphology of salbutamol sulphate was examined by using a DSM 926 scanning electron microscope (Zeiss, Jena, Germany). The powders were mounted onto a plate and were sputter coated with 60 nm gold/palladium using a E5100 Cool Sputter Coater (Polaron, Watford, England).

2.2.5. Thermal analysis

Thermoanalytical studies were performed with a Mettler Toledo DSC 820 Differential Scanning Calorimeter (Giessen, Germany). Samples (~10 mg) were weighted into 40 μl aluminium pans and sealed with a punched aluminium lid. Thermal curves were recorded with a heating rate of 5–10 K/min in a temperature range from 25 to 320°C under a dry nitrogen purge (80 ml/min).

2.2.6. Isothermal microcalorimetry

The powder was investigated using a Thermal Activity Monitor (Type 2277, Thermometric, Sweden) at 25°C. The samples were weighted into a glass ampoule and a tube containing a saturated salt solution ($Mg(NO_3)_2 \times 6\ H_2O$) was added. The ampoule was sealed and equilibrated in the calorimeter for 5 min before lowering it into the measuring site.

2.2.7. Dynamic vapour sorption

Isotherms of water sorption were recorded using Dynamic Vapour Sorption (Porotec Frankfurt, Germany). The samples had an approx. weight of 150 mg. The humidity was varied between 0 and 95% RH at 25°C.

3. Results and discussion

3.1. Characterisation of unmilled salbutamol batches

Scanning electron micrographs show needle-like structures. The needles of salbutamol sulphate are arranged in loose groups or they appear individually. Agglomerates are extremely rare. Each single needle shows a structure with several layers and is approx. 10 μm measured crossways (Fig. 2a). The largest particles can reach up to 120 μm lengthways. There are no apparent differences between the three batches of salbutamol sulphate raw materials concerning their particle size distributions.

3.2. Ball milling of salbutamol sulphate

Powder laser diffraction measurements showed that following 10 min of grinding an effective reduction of particle size was obtained (Table 1). However, there was no dependence of the particle size distribution on grinding times. Irrespective of the duration of grinding it was not possible to decrease the particle size such that only a negligible fraction was larger than 15 μm in diameter. On the contrary, with increased times of grinding, the portion of coarse particles increased. A possible explanation for this phenomenon could be the simultaneous recrystallisation of the amorphous material and therefore particle growth. This resulted in compact forms of agglomerates (Fig. 2b). While the milling process the powder was exposed to ambient moisture and afterwards, while the storage, it was exposed over phosphorus pentoxide.

3.2.1. Thermal analysis

The material which was subjected to the longest period of stress (5 h) had the highest recrystallisation energy (Table 2). The DSC scan of this material corresponded to that of amorphous salbutamol sulphate which had been produced by freeze-drying and subsequent exposure to ambient humidity for about 2 h. A glass transition was not visible

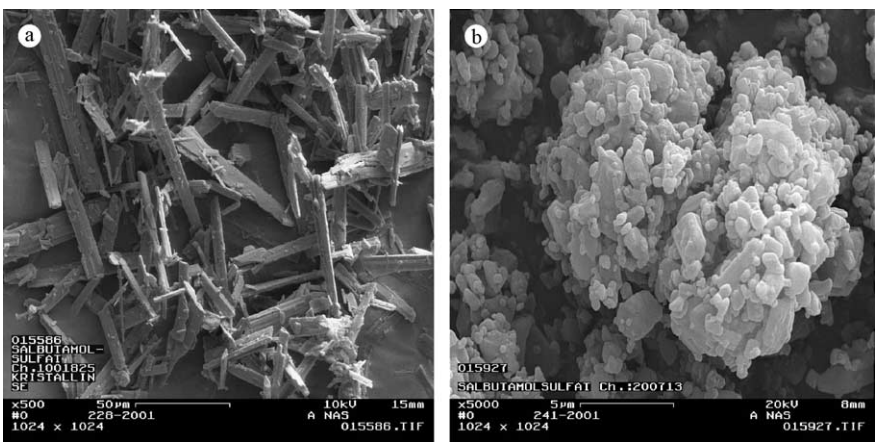

Fig. 2. Scanning electron micrographs illustrating salbutamol sulphate raw material (a) and agglomeration of fine particles after grinding with a ball mill (b).

Table 1
Particle size distribution in dependence on time of grinding

Time of grinding	Particle size of powder sample in μm		
	10% <	50% <	90% <
Raw material	1.86	8.63	34.00
Ball mill (5 h)	0.59	1.88	21.48
Ball mill (1 h)	0.59	1.85	17.24
Ball mill (10 min)	0.64	2.28	11.10

under the employed experimental conditions, which started at 25°C. There was an exothermic recrystallisation peak with an onset temperature of 82°C. The material started to melt at 197°C (Fig. 3).

Shorter milling times resulted in a decrease in recrystallisation energy and a downward shift in the temperature at which the exothermic effect occurred (Fig. 3). Differences in the temperature of recrystallisation can be explained by the fact, that the sample with the highest amorphous amount needs more energy to change to the thermodynamic stable state.

The DSC scan of material which was only milled for 10 min showed no evidence of amorphous material. The limit of detection was 10% amorphous regions.

3.2.2. Isothermal microcalorimetry

By preparing mixtures with 100% crystalline and 100% amorphous material (produced by freeze-drying) a calibration curve for the heats of crystallisation versus known amorphous content of the mixtures can be produced. This curve is used to quantify the unknown amorphous content of micronised particles (Fig. 4).

The calibration curve which has been plotted for salbutamol sulphate enables the level of amorphous material to be determined from the magnitude of the enthalpy change. The values used to prepare this curve were obtained at a relative humidity of 65%. In the studies carried out on mechanically produced (ball-milled) material, the RH was reduced to 53% in order to ensure there was some baseline prior to the recrystallisation event even in cases where the amorphous content was low. Recrystallisation took much longer to occur in the physically produced (freeze-dried) material than in the mechanically-produced material.

Table 2
Energy of recrystallisation of amorphous salbutamol sulphate depending on duration of grinding

Time of grinding in minutes	Energy of recrystallisation in J/g
300	24.0
60	5.8
30	2.6
20	1.9
10	ND

ND, not determined.

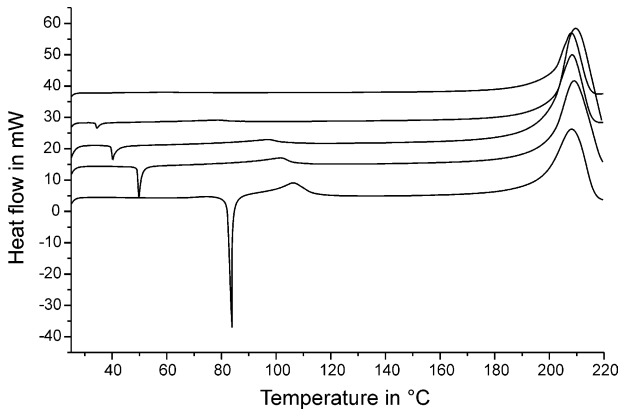

Fig. 3. DSC-Thermograms: (from top to bottom) grinding time 10, 20, 30, 60 min, 5 h.

The reason for this observation is that mechanically-produced amorphous material is found only on the surface of the individual particles, with the result that water sorption can occur more rapidly.

The magnitude of the enthalpy change was not dependent on the relative humidity employed.

In order to further delay recrystallisation, the substance was dried over phosphorus pentoxide in a desiccator after milling.

It could be shown that the drying process affects only the time to recrystallisation and not the recrystallisation energy released (Fig. 5).

Relative humidity, temperature and time of drying were kept constant. The sample with the lowest content of amorphous material has the lowest heat flow, which explains the difference in peak areas observed (Fig. 6). Differences in the time of recrystallisation can be explained by the fact, that the sample with the highest amorphous amount needs the longest time for the sufficient adsorption of water molecule as plastiziser.

3.2.3. Dynamic vapour sorption

Crystalline salbutamol sulphate did not adsorb water to a measurable extent, which could be seen by DVS method

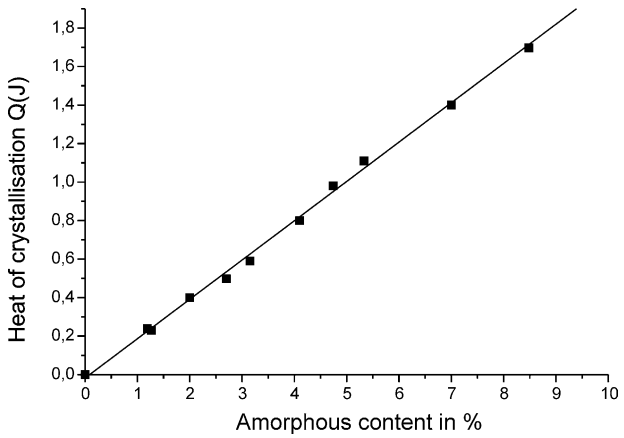

Fig. 4. Calibration plot for salbutamol sulphate.

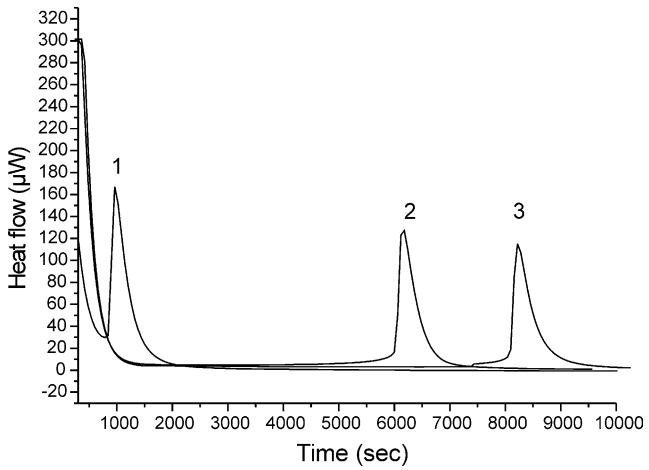

Fig. 5. Effect of drying of amorphous salbutamol sulphate over phosphorous pentoxide on the recrystallisation time (1, directly after micronisation; 2, dried 3 h over phosphorous pentoxide; and 3, dried 8 h over phosphorous pentoxide).

(Fig. 7). When the substance was milled for 10 min, however, a continuous increase in weight was seen up to 55% RH indicating that water molecules are adsorbed by the amorphous surface. As long as sufficient water is available, recrystallisation (which is characterised by a sudden weight loss) occurs (Fig. 7).

3.3. Micronisation

3.3.1. Verification of the critical grinding parameters

In order to assess the effect of the critical milling parameters on the micronised product, a total of 28 trial millings using varying feed rates, feed pressures and grind pressures were carried out on three batches of the raw material. The feed pressure was varied between 6.5 and 8.5 bar and the grind pressure between 4 and 8 bar, respectively. Feed rates were also varied. Mean feed rates were between 1.85 and 26 g/min.

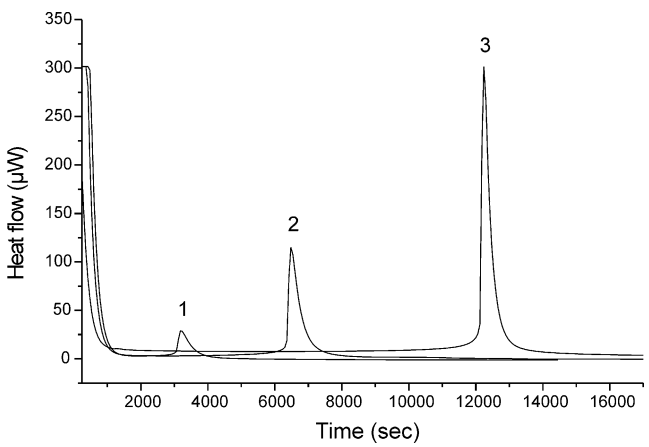

Fig. 6. Isothermal microcalorimetry of 1% amorphous (1); 5% amorphous (2); and 22% amorphous (3) salbutamol sulphate.

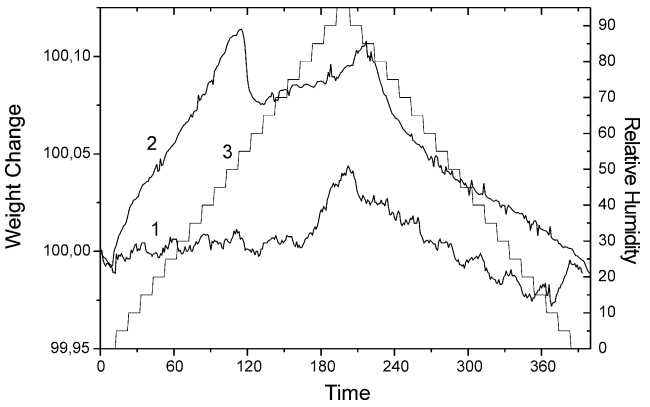

Fig. 7. Moisture sorption of the crystalline material (1) compared with powder ground in a ball mill for 5 min containing 1% amorphous material (2). Curve 3 represents the relative humidity at the respective time points.

It was found that, within the range tested, the feed pressure had no significant effect on the result. When the feed pressure drops below a certain limit, however, clogging could occur, which would result in blowback and unwanted discharge of the product.

Unlike the feed pressure, the grind pressure has a significant effect on the result. Initially, particle size decreased markedly as the grind pressure increased. Pressures of less than 6 bar were not sufficient to obtain the required particle size distribution. There was a marked difference between the effects observed at 5 versus 6 bar (Fig. 8). Too low grind pressures are not sufficient in terms of particle size reduction because they do not give rise to sufficient micronisation energy. At 6 bar and above, the effect of the grind pressure decreased. The reason for this is that, once a certain pressure has been reached, no further increase in the maximum jet speed can be obtained (which is sonic velocity if normal nozzles are used).

Compared to the grind pressure, the feed rate did not have that much of an effect on the micronisation energy. There was a slight tendency for an increase in particle size with increasing feed rate; this applied particularly to particles in the medium size range. Increasing the feed rate increases the concentration of product in the grinding chamber and decreases the interparticulate acceleration distance, thus giving rise to coarser particles.

To achieve the best possible particle size distribution for salbutamol sulphate with the MC 50 Jetmill the following parameters have been determined as optimal: feed pressure, grind pressure and feed rate 7.5 bar, 6 bar and 2.5–5 g/min, respectively.

3.3.2. Particle size analysis and morphology

Laser diffraction is not suitable for the particle size analysis of absolute values of needle shaped particles, but it is possible to evaluate the relative values as a comparison because of the particle adjustment in all directions in the laser beam. The diameters are expressed by volume.

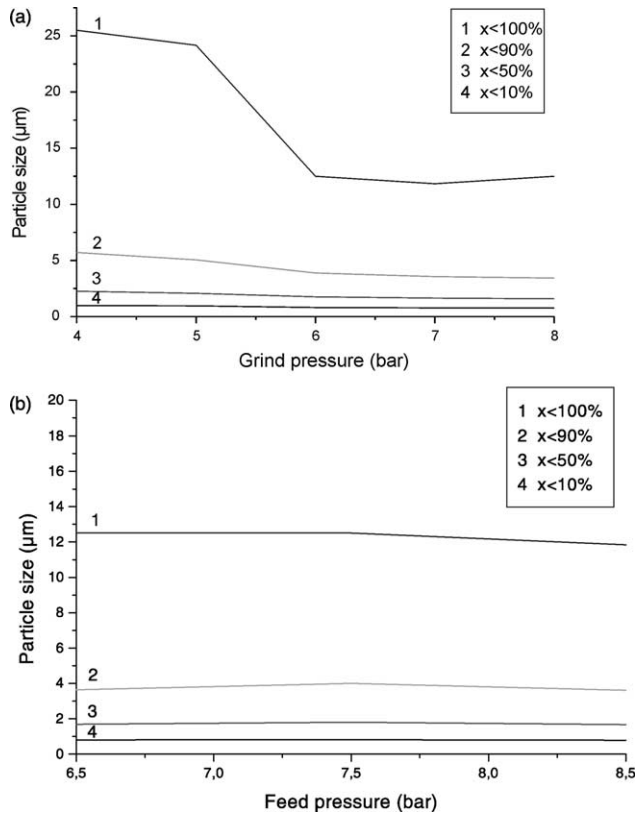

Fig. 8. Dependence of the particle size distribution on the grind pressure (a) and feed pressure (b).

The particle sizes of micronised salbutamol sulphate were similar, irrespective of the raw batches employed as starting material. Therefore a dependence of the raw material on the quality of the powder could not be evaluated. Representative particle size distribution of a micronised batch in comparison with the particle size distribution of the raw material is shown in Fig. 9. The particle size distributions of the milled and unmilled powder was monomodal.

Table 3
Influence of the collecting points on the particle size distribution

Collecting point	Particle size of powder sample in µm		
	10% <	50% <	90% <
Collection chamber	0.79	1.71	3.68
Collection chamber + Mill bag	0.75	1.62	3.53
Mill bag	0.58	1.39	3.36

As mentioned previously, two collecting points in the MC Jetmill 50 have to be taken into account: the main quantity of micronised particles in the collection chamber on the one hand, and the fine particles in the mill bag on the other. The data in Table 3 show the different particle size distributions depending on the collecting points. The finest particles are deposited in the mill bag.

Scanning electron micrographs of the micronised powders show irregular-formed, partly smooth-faced particles with sizes of approx. 0.25–13 µm (Fig. 10). Several of the particles are agglomerated. Agglomerates are 15–140 µm in diameter. These are loose agglomerates which can be easily redispersed. The larger part are very fine particles (<1 µm), that tend to cohesion as a result of their electrostatic charge.

3.3.3. Isothermal microcalorimetry

DSC is not sufficiently sensitive to quantify the amorphous content in micronised salbutamol sulphate. For this purpose isothermal microcalorimetry is the method of choice.

The experiments are carried out at a relative humidity of 53%. A shoulder follows the sharp recrystallisation peak.

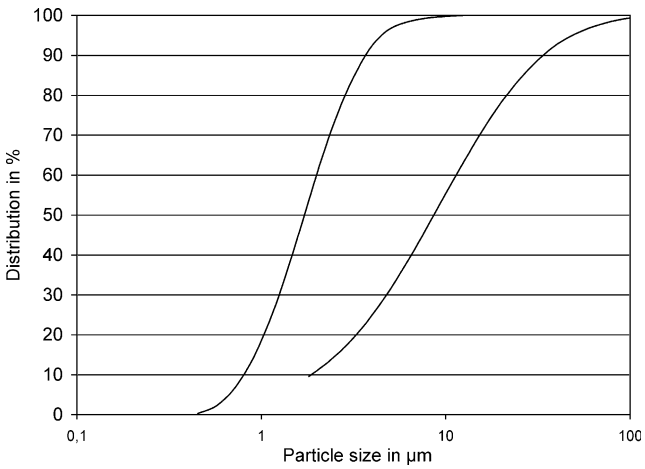

Fig. 9. Representative particle size distribution of milled (left) and unmilled salbutamol sulphate (right).

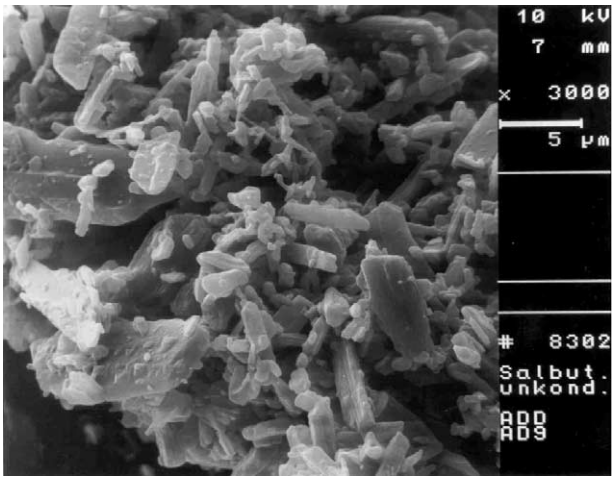

Fig. 10. Scanning electron micrographs illustrating agglomerates after micronisation.

Table 4
Influence of the grind pressure on the amorphous content

Grind pressure (bar)	4	5	6	7	8
Amorphous amount (%)	3.5	4.7	5.3	5.6	6.3

Similar observations have been made in the case of lactose [15]. In the case of lactose, the thermodynamic transition can be explained by the transformation of the metastable anhydrate form of α-lactose into the stable monohydrate form. An alternative explanation for the exothermic effect can be given by the recrystallisation kinetics where water sorption at low humidity is a slow process (thermodynamic versus kinetic control).

The quantity of the amorphous content of salbutamol sulphate can be determined from a calibration curve of amount of amorphous material present in the sample versus the microcalorimetric signal. A dependence of the amorphous content on the feed pressure and the feed rate is not verifiable whereas a clear increase of the amorphous parts caused by a higher grind pressure was obvious: the higher the grind pressure, the more micronisation energy is transmitted on the particles and the more crystal structures on the particle surface are being destroyed, which leads consequently to a higher quantity of amorphous parts.

The values given in Table 4 relate to the product taken from the collecting chamber only.

When the product mixture was taken out of the collecting chamber and the mill bag an amorphous content of 6.9% can be established at a pressure of 6 bar. If the sample is taken from the mill bag only, 14% of the entire quantity are amorphous.

This would point to the fact, that mostly the fine particles have disordered regions on their surface.

3.3.4. Dynamic vapour sorption

The micronised powder of salbutamol sulphate shows, analogous to the pilot tests with a ball mill, clear differences in the sorption behaviour compared with the crystalline raw material. There is an initial absorption of water up to a level of 55% RH followed by spontaneous recrystallisation of amorphous regions and expulsion of water (data not shown).

Apart from the isothermal micro-calorimetry the DVS-method is likewise suitable for the assessment of the crystallinity after micronisation and during storage.

4. Conclusion

It was possible to produce respirable particles of salbutamol sulphate with an air-jet-mill.

Optimisation of the micronisation process was necessary with respect to minimising the amorphous content of the drug while simultaneously achieving satisfactory particle size reduction.

The grind pressure was of utmost importance with respect to particle size distribution and the physical powder stability. For salbutamol sulphate, ground with a MC Jetmill 50, an grind pressure of 6 bar was optimal. Pressures below 6 bar were not sufficient to produce the required reduction in particle size. Pressures above 6 bar mainly led to an increase in the amorphous content without changes in the particle size distribution. The amorphous content correlated well with the energy input during micronisation. An excess of energy input caused additional destruction of the crystallinity structure on the particle surface, without further improvement in particle grinding. Under such optimised micronisation conditions an amorphous content of 6.9% on average was generated for salbutamol.

The feed rate had a negligible influence on the powder quality. Increasing the feed rate increased the concentration of product in the grinding chamber and decreased the interparticulate acceleration distance, thus giving rise to coarser particles. The feed pressure had no critical influence on the particle size.

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