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RESEARCH PAPER

# Conditioning Following Powder Micronization: Influence on Particle Growth of Salbutamol Sulfate

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## ABSTRACT

Micronization is a high-energy process that induces changes in the crystallinity of materials. As a result, the crystalline structures on the particles' surface are being destroyed and amorphous areas are formed. After micronization of salbutamol sulfate to be used in dry powder inhalers, only small amounts of amorphous material are produced. Nevertheless, even these small amounts can have important effects on the physical stability of the powder. The amorphous state is thermodynamically unstable and tends to convert to the stable, crystalline state. The recrystallization process of disordered regions on the particles' surface leads to particle growth of milled particles. In this case, bridges of solid material are being formed between the individual particles, which leads to particle growth. This is an undesirable process, because particles for pulmonary administration are designed to range between 1 and 10 μm in diameter to exert respirative effect. In the present investigation, salbutamol sulfate is micronized by an air jet mill, and the generated products are exposed to different conditions. Thereafter, the best possible conditioning parameters and storage conditions for the micronized salbutamol sulfate are worked out and rated. The aim of this treatise is to demonstrate the importance of conditioning following micronization.

*Key Words:* Dry and wet conditioning; Storage; Salbutamol sulfate.

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## INTRODUCTION

In some pharmaceutical processes, such as grinding, wet granulation, tablet compaction, and spray drying, disorder of crystal structure can occur and may lead to amorphous particles or parts thereof. Amorphous regions demonstrate rheological properties of a solid state and the structure of a liquid.[1] Because of their higher state of energy, they are thermodynamically unstable and tend to convert to a stable, crystalline state. This reaction—when it occurs in a pharmaceutical preparation—is frequently being regarded as undesirable, because the amorphous drug particles may change their properties on storage. In previous publications, analytical methods for the detection of amorphous material in pharmaceutical systems were introduced.[2–5] Processes leading to changes in crystallinity also were described,[6] and the significance of these findings for pharmaceutical systems were discussed.[7,8] Until the present, sparse information on appropriate handling of amorphous solids with the aim of achieving a thermodynamically stable product has been published.

In the study described here, partly amorphous salbutamol sulfate is formed as a result of micronization with an air jet mill. Air jet micronization represents an important step for the manufacture of constituents of dry powder inhalers. Depending on the level of grinding energy, increasing fractions of amorphous material may be generated on the surface of the crystal. Problems with respect to uncontrolled particle growth may arise in those instances when the recrystallization of the micronized material proceeds in an uncontrolled manner (e.g., during arbitrary storage conditions of the pharmaceutical powder). This may have serious consequences with respect to the effectiveness of powders for inhalation, because particle growth may generate fractions of the particles with diameters outside of the respirative range (between 1 and 10 μm).

One of the techniques towards achievement of micronized powders with improved physicochemical stability is the introduction of a conditioning step following their micronization. During this process, the amorphous parts are converted into crystalline solids under storage conditions that are controlled with respect to relative humidity and temperature. These conditions aim at reducing the glass transition (*Tg*) of the solid material by the adsorption of water[9] and setting the surrounding temperature to values above *Tg* so that the molecular mobility and, consequently, the recrystallization process is accelerated.[10]

In this treatise, the influence of conditioning parameters for micronized salbutamol sulfate is investigated systematically according to Sch. 1 to discover optimum conditioning parameters for the rapid and entire conversion of amorphous to crystalline material with minimum particle growth.

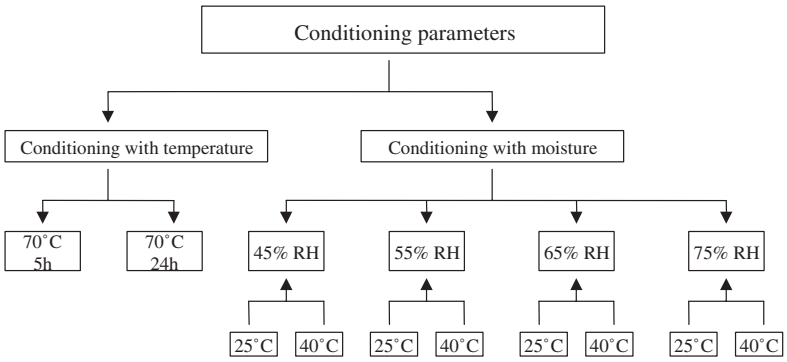
## MATERIALS

Salbutamol sulfate (batch Nos. 200713, 200921, and 1001825) was supplied by Boehringer Ingelheim Pharma GmbH&Co. KG (Ingelheim, Germany). As packaging materials, a polyethylen bag, a polyethylen bag within an aluminium bag, and a twist-off-Glass were used.

## METHODS

### Milling

Micronized powders were prepared with a MC Jetmill 50 (Jetpharma, Balerna, Switzerland). Extant room conditions were 21°C ± 1°C and 45% ± 2% RH.




***Scheme 1.*** Systematic evaluation of conditioning parameters for micronized salbutamol sulfate.

### Conditioning

The micronized powders underwent different conditioning settings in a climate chamber (Weiß Klimatechnik GmbH, Reiskirchen-Lindstruth, Germany). The temperature was set at 25°C and 40°C, and the relative humidity was varied between 45% and 75%, respectively. For ''dry'' conditioning settings, the powders were prepared at a temperature of 70°C in a thermal oven (Heraeus, Hanau, Germany).

### Recording of Humidity

The sorption behavior of the micronized and wrapped powder was measured by using a humidity sensor (Ebro, Ingolstadt, Germany).

### Particle Size Analysis

The particle size distributions of salbutamol sulfate were measured by using powder laser diffraction with a Helios-System (Sympatec, Clausthal-Zellerfeld, Germany). Samples were introduced through the Rodos dry powder feeder. The supply pressure of the injector was set at 3 bar. The optical concentration reached values between 4% and 8%.

### Particle Morphology

The morphology of salbutamol sulfate 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.

### 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 was added containing a saturated salt solution. The ampoule was sealed and equilibrated in the calorimeter for 5 min before lowering it into the measuring site.

### Powder X-Ray Diffraction

The Powder X-Ray Diffraction (Bruker, Rheinstetten, Germany) patterns were acquired at different temperatures using Cu-K $\alpha$ radiation ($\lambda = 1.5406$ Å). The data were collected over an angular range of 2–40° $2\theta$ using a step size of 0,014° $2\theta$ and a step time of 2 s.

## RESULTS AND DISCUSSION

### Conditioning with Elevated Temperature (''Dry'' Conditioning)

Conditioning of the micronized salbutamol sulfate for a duration of 5 hr at 70°C did not lead to recrystallization, and therefore no stable product was formed. Such conditions have been identified as counterproductive rather, since water was expelled from the sample due to the high temperature. Water in this case serves as a plastisizer and consequently its disappearance leads to a stabilization of the amorphous state (increase in *Tg*). Therefore, no changes in the amorphous content were observed under such conditions.

With the use of isothermal microcalorimetry it was shown that the exothermal recrystallization process was delayed on account of the water displacement (Fig. 1). An increase of the thermal conditioning time for a duration of up to 24 hr had no additional effect.

Particle growth was not observed following dry conditioning. This is shown in Table 1.

With the use of x-ray powder diffractometry in vacuum and at different temperatures, it was demonstrated that amorphous salbutamol sulfate (produced by freeze-drying) did not recrystallize under exclusion of humidity (Fig. 2). Therefore, water molecules are necessary for the transformation into the thermostable state. Consequently, minimum relative humidities are essential to initiate and maintain the recrystallization process.

### Conditioning with Moisture (''Wet'' Conditioning)

By using isothermal microcalorimetry it has been found that relative humidities below 50% at 25°C were insufficient to achieve complete recrystallization of amorphous salbutamol sulfate within 24 hr. For

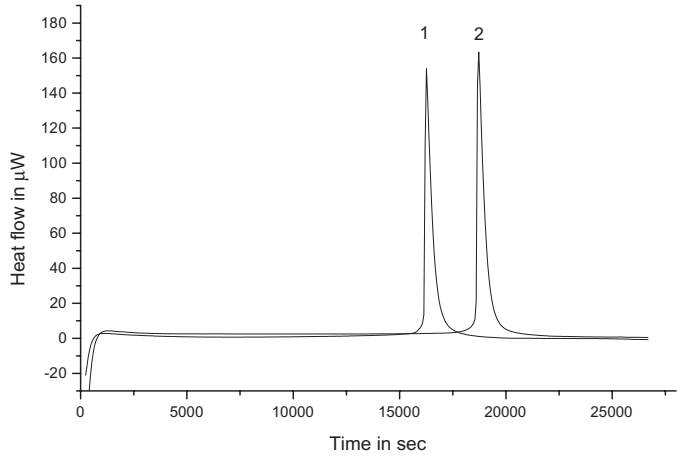



***Figure 1.*** Isothermal microcalorimetry of a freshly micronized powder (1) and one of a dry conditioned powder at a temperature of 70°C for 5 hr (2).

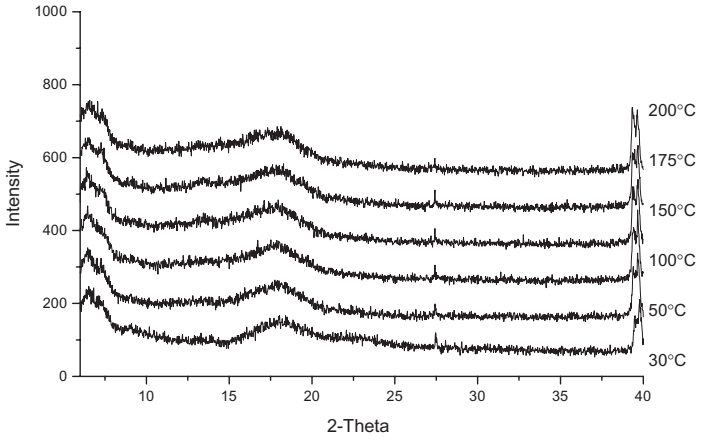



***Figure 2.*** X-ray powder diffractometry of 100% amorphous material at different temperatures under vacuum. The material was stored at room temperature under $P_2O_5$.

***Table 1.*** Particle size distribution after dry conditioning of micronized salbutamol sulfate.

| | Micronized powder (µm) | Micronized powder conditioned for 5 hr at 70°C (µm) | Relative change of particle size spreading (%) |
|---|---|---|---|
| <10% | 0.83 | 0.82 | −1.2 |
| <50% | 1.94 | 1.90 | −2.1 |
| <90% | 4.53 | 4.45 | −1.8 |

example, conditioning of a sample for a 24 hr time period at 25°C and 45% RH lead to a reduction of the amorphous fraction by only 2.5% at an initial content of amorphous material of 7.7%.

When more appropriate conditioning settings by increasing the relative air humidity were used, complete recrystallization occurred; however, particle growth was inevitable in each batch investigated. The particle growth was attributed to the formation of bridges between the amorphous surfaces that took place during the recrystallization process.

By means of selective variation of humidity and temperature, the percentage of particle growth was studied. A clear tendency toward stronger particle growth was observed by an increase in relative humidity (Table 2). For example, the relative change in particle size distribution of the fraction below the 50th percentile increased from 8.5% at 55% RH and 25°C to 15.0% at 65% RH and 25°C. A less pronounced effect on particle growth was

***Table 2.*** Dependence of particle growth on the relative humidity and temperature during conditioning.

| | Micronized powder (μm) | Micronized powder conditioned (μm) | Relative change in particle size distribution (%) |
|---|---|---|---|
| 24 hr 55% 25°C | | | |
| <10% | 0.70 | 0.78 | 11.40 |
| <50% | 1.30 | 1.66 | 8.50 |
| <90% | 3.42 | 3.56 | 4.10 |
| 24 hr 65% 25°C | | | |
| <10% | 0.70 | 0.82 | 17.10 |
| <50% | 1.53 | 1.76 | 15.00 |
| <90% | 3.42 | 3.67 | 7.30 |
| 24 hr 75% 25°C | | | |
| <10% | 0.70 | 0.83 | 18.60 |
| <50% | 1.53 | 1.77 | 15.70 |
| <90% | 3.42 | 3.69 | 7.90 |
| 24 hr 55% 40°C | | | |
| <10% | 0.70 | 0.79 | 12.90 |
| <50% | 1.53 | 1.68 | 9.80 |
| <90% | 3.42 | 3.59 | 5.00 |
| 24 hr 65% 40°C | | | |
| <10% | 0.70 | 0.80 | 14.30 |
| <50% | 1.53 | 1.72 | 12.40 |
| <90% | 3.42 | 3.64 | 6.40 |
| 24 hr 75% 40°C | | | |
| <10% | 0.70 | 0.84 | 20.00 |
| <50% | 1.53 | 1.78 | 16.30 |
| <90% | 3.42 | 3.69 | 7.90 |

observed by an increase in the conditioning temperature from 25°C to 40°C at constant relative humidities (Table 2).

Following conditioning for a 5-hr time period at 40°C and 75% RH, a sample of partially amorphous powder was completely converted into crystalline material. Prolongation of the duration of the conditioning process beyond 5 hr had no additional effect on the particle size distribution. Thus, it may be concluded that the final stage of the conditioning process was already reached after 5 hr (Table 2).

In summary, it has been shown that dry conditioning was not a feasible approach. The more important factor was the relative humidity, which should be maintained at 55% at room temperature for the product to recrystallize within 24 hr. This humidity level showed the smallest influence on particle growth. The most rapid conditioning was achieved at 40°C and 75% RH where a stable, entirely crystalline product was obtained already after 5 hr of treatment but with the largest increase in particle size.

## Physical Stability on Storage

### Storage Following "Dry" and "Wet" Conditioning

Using the methods described above, it was shown that the physical stability of the product on storage under normal storage conditions (i.e., 22°C ± 2°C; 50% ± 8% RH) was dependent on the parameters of a preceding conditioning step. With dry conditioning, uncontrolled particle growth up to 16% in terms of particle diameter was observed following 4 weeks of storage. Humid conditioning as pretreatment of the freshly milled material on the other side resulted in products that remained stable throughout the storage period (Fig. 4).

### Storage Without Preceding Conditioning Step

The assessment of particle growth of nonconditioned material was conducted under different methods of storage. When freshly micronized powder was stored in an open TWO-Glass at 21.5°C and 42% RH, the use of isothermal microcalorimetry indicated a gradual loss of amorphous content in the sample over a storage period of 4 weeks (Fig. 3). When salbutamol sulfate—stored in a simple PE-bag—was evaluated for its amorphous content at different storage times, a continuous decrease was observed. Recrystallization was significantly minimized when micronized salbutamol sulfate was wrapped in a PE-bag plus an aluminum bag. This observation can be explained by the fact that the latter packaging material showed the least overall water permeability.

To assess particle growth of nonconditioned samples during storage, 50 g of freshly micronized material was wrapped in a PE-bag and stored at 22°C ± 1°C and 45% ± 5% RH for a total period of 3 months. After 1, 2, and 4 weeks as well as after 3 months, samples were collected and analyzed for their particle size distribution and amorphous content. The powder treated under these conditions showed significant particle growth.

By incorporating a humidity sensor into the PE-bag, the sorption behavior of the micronized powder was monitored. For this experiment, ~30 g

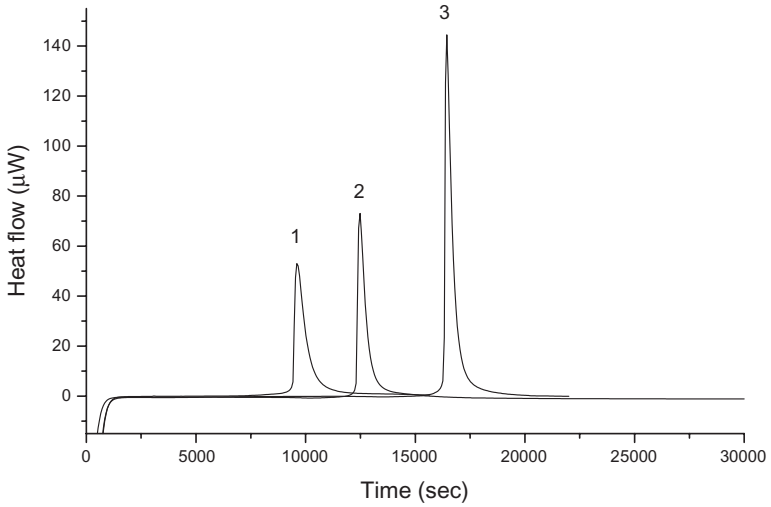



***Figure 3.*** Microcalorimetry of micronized unconditioned salbutamol sulfate on storage in an open TWO-Glass at room temperature (21.5°C, 42% RH): Amorphous amounts following 1 (3), 2 (2), and 4 (1) weeks of storage. The amorphous contents were 6.5%, 5.4%, and 4.5% following storage for 1, 2, and 4 weeks, respectively.

of freshly ground material were wrapped in a PE-bag together with a humidity sensor. The bag was closed and stored at $22^{\circ}C \pm 1^{\circ}C$ and $45\% \pm 5\%$ RH. Analysis of the water sorption of micronized salbutamol sulfate stored under these conditions is shown in Fig. 5. Initially, the relative humidity in the closed bag was very low. This can be explained by the adsorption of water to the amorphous areas on the particle surfaces. Within 5 days, ambient humidity was reached inside the bag. Because the relative humidity was less then 50%, the process of recrystallization took place only at a comparatively slow rate.

The recrystallization did not proceed as a cooperative process. Rather, the amorphous material assimilated water, recrystallized, and the desorbed water molecules were being assimilated by further amorphous regions. This mechanism can be deduced from the oscillating shape of the time course of relative humidity within the bag (Fig. 5).

An analogous storage experiment was conducted at the same temperature of $22^{\circ}C \pm 1^{\circ}C$ but at a humidity level of 55%. Here, a clear difference in the sorption behavior was evident (Fig. 6). The relative humidity within the bag increased up to ~55%, followed by a rapid increase in humidity level up to 98%, and final adjustment to the equilibrium moisture content of ~55%. The rapid increase in humidity levels up to 98% was due to the recrystallization of the amorphous salbutamol sulfate in the presence of water, followed by the desorption of water after the recrystallization process. The decline of relative humidity after 2–3 days can be interpreted by the diffusion of water out of the PE-bag. Under such storage conditions, the sample was completely recrystallized within 1 week.

Thus, it has been shown that during storage of the micronized powder a "self-conditioning" process may occur. The rate of self-conditioning was dependent on the relative humidity in the storage chamber. Lower humidity led to an extended duration of the self-conditioning process. Furthermore, when particles were stored below a relative humidity of 50%, a significantly lower particle growth than particles that were stored above this humidity value was observed.

## CONCLUSIONS

Sufficient conditioning of salbutamol sulfate ensured the complete and controlled conversion of amorphous parts into crystalline material and a stabilization of the powder. The physical stability of the micronized powder was influenced by the conditioning parameters. Dry conditioning has been shown to be useless in this regard. The relative humidity at room temperature should be at least 55% so that the powder will recrystallize within a period of 24 hr. This humidity level showed the smallest particle growth under the conditions tested. When shorter conditioning periods are desired, conditioning at 40°C and 75% RH have been shown to be alternative

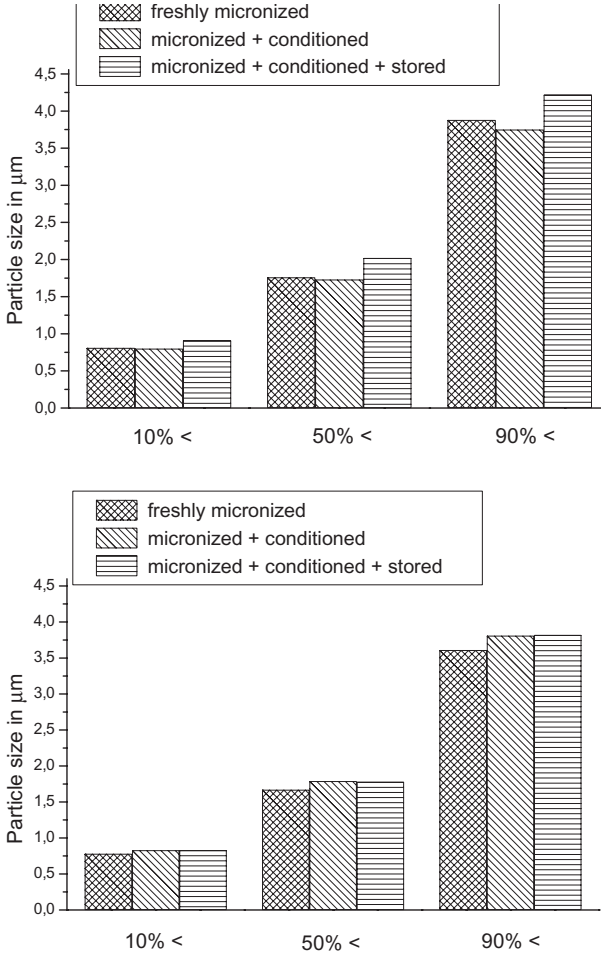



***Figure 4.*** Particle size distributions of micronized, dry conditioned (upper figure) and humid conditioned (lower figure) salbutamol powder following storage for 4 weeks. The humid conditioning parameters were 21°C at 55% RH for 24 hr. The dry conditioning parameters were 70°C for 5 hr. The storage conditions were 22°C ± 2°C; 50% ± 8% RH. Approximately 50 g of salbutamol sulfate were stored in a PE-bag in each case.

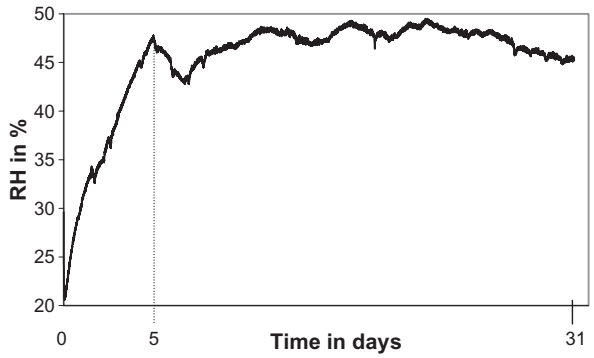



***Figure 5.*** Relative humidity in a PE-bag filled with freshly micronized salbutamol sulfate powder and stored at relative humidity of 45%.

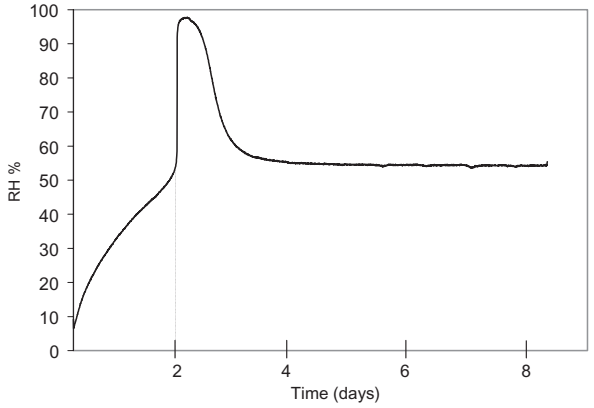



***Figure 6.*** Relative humidity in a PE-bag filled with freshly micronized salbutamol sulfate powder and stored at relative humidity of 55%.

conditions to obtain a stable, entirely crystalline product.

The advantage of optimized conditioning process parameters is that every batch can be controlled to show a relatively small but acceptable particle growth. However, particle growth, cannot be completely prevented. The kinetics of the process is depending on the relative humidity, with higher humidities favoring faster rates. The extent of the agglomeration is dependent on the amorphous parts and, therefore, on the micronization energy, but also on the parameters of conditioning and storage. The use of nonconditioned material implies the inherent risk of its uncontrolled recristallization, which may occur at any time following milling (i.e., during storage of the milled material), formulation of the powder for dry powder inhalers, or following manufacture of the product even as late as in the hands of the patient.

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