The use of moisture sorption technique in quantification of the degree of disorder in micronized salbutamol sulphate

Mykhaylova V., Gorny M., Jakobs M., Urbanetz N.A
Institute of Pharmaceutics and Biopharmaceutics,
Heinrich-Heine-University, Universitaetsstraße 1, 40225 Duesseldorf, Germany

Dry powder formulations used for pulmonary application are preferably prepared using crystalline powders, because the crystalline state is thermodynamically stable. To ensure that the drug will be presented to the lower respiratory tract, especially the alveolar region, the aerodynamic diameter of the particles has to be between 0.5 and 5µm. That is why the drug has to be micronized. During the milling process the crystalline structure may be destroyed. Generated amorphous areas are mainly located at the surface of the particles. As a consequence bioavailability, physical stability and hygroscopicity of such partly amorphous particles may be affected, since during the storage transformation to the thermodynamically stable crystalline state may take place. Therefore it is not only important to determine the amorphous content but also to quantify the amount of amorphous areas in micronized drug.

The amount of the amorphous material can be quantified using techniques like X-ray diffraction, differential scanning and isothermal calorimetry. The quantification limit of these methods varies between 10% and 1% depending on the chosen method. It has been reported that the quantification limit can be reduced down to 0,125% by using moisture sorption. The aim of this study is to determine whether moisture sorption can be used for the quantification of the amorphous amount in micronized salbutamol sulphate [1].

Eleven different blends containing 0% to 100% amorphous salbutamol sulphate were produced using the Turbula shaker mixer (Willy A. Bachofen AG Maschinenfabrik, Switzerland). Amorphous powder was prepared by spray-drying an aqueous salbutamol sulphate solution in a mini spray dryer B-191 (Büchi Labortechnik GmbH, Switzerland). Micronization of crystalline salbutamol sulphate was performed in an air jet mill (50AS, Hosokawa Alpine AG, Germany).

Samples, approximately 2 g quantities were examined by the moisture sorption system SPS11 (Project Messtechnik, Germany). The most important part of this system is the humidity and temperature controlled chamber as well as a quite precise and sensitive balance. The balance measures weight changes of the samples exposed to a defined humidity program. The amorphous state possesses a higher potential to absorb moisture than crystalline materials. That leads to higher water uptake at a defined relative humidity in comparison to the crystalline material. Due to the instability of the amorphous state the powder tends to recrystallisation during the raising of the relative humidity. This can be explained by the fact that the absorbed water acts as a plasticizer. The recrystallization is accompanied by a loss of water and associated with a mass decrease. The increase and decrease of mass can be gravimetrically detected and may be used to quantify the amount of amorphous material in the sample.

At the beginning of the measurements the relative humidity (RH) was set to 0%. In steps of 10% the relative humidity was raised to 90% and finally to 95%. Subsequently the RH was decreased to 0% the same way. This cycle was repeated once more. The temperature was set to 25°C and the samples were weighed in time intervals of 6 minutes.

The correlation between the weight change and the percent of amorphous amount in the samples was determined. Different methods to generate a calibration curve were tested and the most suitable for the quantification of the amorphous amount in micronized salbutamol sulphate has been isolated.

References:

[1] Gorny M., Jakobs M., Mykhaylova V., Urbanetz N.A.; Quantifying the degree of disorder in micronized salbutamol sulphate using moisture sorption analysis, *submitted*