Impact of Flow Rate and Exposure Time on Humidity-Induced Crystallization of Salbutamol Sulphate

Daniel J. Burnett,1 Armando R. Garcia, Jerry Y.Y. Heng,2 and Frank Thielmann2
1Surface Measurement Systems Ltd., 2125 28th Street SW, Suite 1, Allentown, PA 18103, USA
2Imperial College London, Department of Chemical Engineering, South Kensington Campus, London SW7 2AZ, UK
~ Email: dburnett@surfacemeasurementsystems.com~

BACKGROUND
The deposition of active ingredients, delivered via dry powder inhalers is known to be affected by the humidity in the lung. Humidity effects can cause a change in the aerodynamic particle size distribution due to hypertonic shrinkage or hypotonic growth [1]. Other factors are agglomeration of particles facilitated by crystallization of amorphous sites on the particle surface. A similar mechanism is also dominant for the condensational growth of nanoaerosol particles in the upper airways [1]. While these factors are well known, it is poorly understood whether the equilibrium between lung humidity and particle surface is fully established. This depends on the inspiratory flow rate and exposure time of a particle in the airways [2]. Especially in cases of agglomeration due to crystallization of amorphous sites the above-mentioned factors strongly affect the crystallization kinetics and therefore the degree of agglomeration/crystallization. This study investigates the flow rate and exposure time dependency of water-induced crystallization of salbutamol sulphate (SS) as a model compound at high humidity.

MATERIALS AND METHODS
SS (Sigma-Aldrich, St. Louis, MO) was spray-dried to obtain particles that are highly amorphous in a respirable particle size range. Gravimetric water sorption experiments have been carried out using the DVS-Advantage instrument (Surface Measurement Systems, London, UK). This instrument measures the uptake and loss of vapor gravimetrically using a recording ultra-microbalance with a mass resolution of ±0.1 μg as shown in Figure 1.

The SS samples (10-25 mg) were placed into the instrument at the desired temperature where they were initially dried in a stream of dry air (< 0.1% relative humidity, RH) for several hours to establish a dry mass. The samples were then exposed to the desired humidity profile while monitoring the sample mass. Several different exposure times at constant flow rates ranging from 2 to 15 min were investigated at a square wave with a plateau of 20% RH followed by an exposure at 95% RH for different durations. Subsequently the RH was put back to 20% RH (Figure 2). In the same manner different flow rates from 100 to 900 ml/min at constant exposure time were investigated.

Amounts of water adsorbed at 20% RH before and after exposure to 95% RH were measured and amorphous content calculated according to methods described in the literature [3, 4].

RESULTS AND DISCUSSION
As can be seen from Figure 2 the samples begin to lose mass once exposed to 95% RH. Water is a common plasticizer for many materials, which can dramatically decrease the glass transition temperature, and for some low molecular weight materials, it causes the amorphous phase to relax and transform to the more stable, crystalline state. Therefore, the net mass loss observed in Figure 2 for the amorphous sample is ascribed to moisture-induced crystallization. This has been observed previously in gravimetric studies [5, 6, 7, 8]. Figure 3 shows the calculated amorphous content as a function of exposure time at 95% RH and flow rates of 500, 750 and 900 ml/min.

The degree of crystallization increases with increasing exposure time at constant flow rate. This is due to the fact that at lower exposure times and lower flow rates there is insufficient time for a full crystallization of the SS sample due to the nucleation kinetics. After 10 min, however, crystallization is almost complete.

When different flow rates are compared at constant exposure time (Figure 4) there was a clear decrease in amorphous content observed at higher flow rates, most likely due to the faster diffusion in the particles on the particle surface, respectively at higher flow rates.

CONCLUSIONS
This study shows that equilibrium between SS particles and a high humidity environment as present in the lung is strongly depending on inspiratory flow rate and exposure time. The lower the flow rate and the shorter the exposure time the less crystallization/agglomeration occurs suggesting that crystallization-induced agglomeration kinetics play an important role in the deposition pattern of DPI products. Another potential impact is on the bioavailability in the lung if a drug changes polymorphic form or changes from amorphous to crystalline form, effectively altering dissolution.

REFERENCES