# CHARACTERIZATION OF TOBRAMYCIN POWDER: SOLID-STATE AND AERODYNAMIC PERFORMANCE INVESTIGATION

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**Purpose**

Tobramycin is an aminoglycoside antibiotic active against Gram-negative bacteria, in particularly Pseudomonas Aeruginosa that often affect the respiratory tract. The administration of antibiotic by inhalation permits to treat directly the infection site, limiting the side effects. To be considered respirable, a powder needs aerodynamic diameter less than 5μm. Moreover, the powder can be affected by solid-state characteristics such different polymorphic phases that influence the quality, stability and aerodynamic performance of drug product. Hence, the solid-state characteristics of three tobramycin raw materials (coded A, B and C) and one spray dried powder containing tobramycin (D) were investigated. Finally, the aerodynamic assessment of the powder D was performed.

**Methods**

The micronized powder was manufactured by spray drying using a hydroalcoholic solution of tobramycin raw material A and a low amount of sodium stearate (1%w/w).

Different tobramycin raw materials and spray-dried powder were characterized in term of differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), X-Ray Powder diffraction, scanning electron microscopy (SEM), Dynamic Vapour Sorption (DVS). Finally, 32 mg of spray-dried tobramycin aerodynamic performance were *in vitro* studied using a RS01® (Plastiape, MI) device through the Next Generation Impactor (NGI). Quantitative determination of tobramycin was performed by HPLC analysis.

**Results**

DSC profiles showed slight thermal events between 40 and 180°C for each powder, but powder A had an endothermic peak at 230 °C followed by an exothermic event indicating a recrystallization and a final melting at 240°C. Powder C had only an endothermic peak at 240 °C. X-ray diffractions confirmed DSC evidences: powders A and C had a crystalline structure, while powder B and D showed amorphous patterns. DVS profiles of powders A and D had a progressive increase in mass with a peak at 80% RH value, instead D presented a mass increase between 40 and 60 % RH and this was interpreted as the consequence of drug crystallization. Losses on drying of powders A, B and C were respectively 6.0%, 5.0% and 5.6% while powder D had a value corresponding to 9.8%. SEM revealed that powder D had a different morphology from raw materials: powders A, B, C presented crystalline surface with rough surface while powder D presented spherical morphology with a smooth surface. The *in vitro* aerodynamic performance of powder D showed a good respirability, since the value of emitted dose, fine particle dose, MMAD were 25.99 ± 0.25 mg, 13.95 ± 0.63 mg and 1.71 ± 0.25 μm, respectively.

**Conclusions**

Tobramycin can exist in different crystal phases; this is an important evidence that must be considered during dry powder inhaler formulations development. Starting from a crystalline powder, in fact, is possible to obtain a powder spray dried with different solid state characteristics that can be change on time and this can influence the powder aerodynamic performances, especially its shelf life.