Spray Dried Pyrazinoate Salts for Tuberculosis Therapy
A. J. Hickey 1, P. G. Durham 1, N. German 1, Y. Zhang 1, D. A. Mitchison 2, P. B. Fourie 3
1 RTI International, 2 St. George's University of London, 3 University of Pretoria

Purpose
The active moiety of the antitubercular agent pyrazinamide is pyrazinoic acid (POA). The action of POA is known to be pH dependent(1). Delivery of POA salts by the pulmonary route may promote their action locally and systemically(2). Selection of salts of POA suitable for presentation under effective conditions would facilitate disease therapy.

Methods
The salts POA-leucine and POA-NH4 were prepared. 10 mg/mL aqueous solutions were spray dried (Buchi B-290). Large porous, low density particles of both salts were observed by scanning electron microscopy. The POA-leucine particles were collapsed hollow spheres with smooth surfaces and small pores. POA-NH4 particles were mostly spherical with a corrugated surface, with a small population of cubic particles. The geometric mean sizes were 3.7 and 4.6 µm for POA-leucine and POA-NH4, respectively, as determined by image analysis (n=100).

Results
Aerodynamic particle size distribution was determined by cascade impaction (Next Generation Impactor, operated at 60 L/min) emitted from a capsule based dry powder inhaler (Aerolizer®). POA-leucine particles were bimodally distributed with a fine particle fraction (FPF < 4.46µm) of 29.7% and a mass median aerodynamic diameter (MMAD) of the fine mode of 1.3 µm (geometric standard deviation (GSD) of 1.75). Peak bimodality was confirmed by Aerodynamic Particle Sizer (TSI Instruments). POA-NH4 particles prepared under the same conditions exhibited a MMAD of 5.4 µm (GSD 1.83) and FPF(4.46) of 14.7%. The emitted dose (ED) from the Aerolizer® was measured by filter deposition utilizing USP Apparatus B for delivered dose uniformity operated at 60 LPM for one minute. ED was 81% and 70% for POA-leucine and POA-NH4, respectively.

Conclusion
Pyrazinoic acid salts were suitable for spray drying and their morphology and particle size was within the range suitable for pulmonary delivery. Further work is required to optimize aerosol dispersion to achieve a unimodal aerodynamic particle size distribution.

References: