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# Spray Dried Pyrazinoate Salts for Tuberculosis Therapy

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## PURPOSE

The active moiety of the antitubercular agent pyrazinamide (PZA) is pyrazinoic acid (POA). In the course of a regular treatment regime, PZA is delivered orally. It is then taken up by *M.tuberculosis*, where it is converted to POA and is removed from the cell. In an acidic extracellular environment, POA is protonated to HPOA (Figure 1), which permeates back into the bacteria, resulting in accumulation and toxicity.[1]

Delivery of POA salts by the pulmonary route may promote their action locally and systemically.[2] Direct lung delivery of dry powders promotes higher pulmonary concentration compared to other routes. POA is acidic (pKa = 2.9) and could further acidify the bacterial extracellular environment, increasing the effectiveness of orally administered PZA (Figure 1). Selection of salts of POA suitable for presentation under effective conditions would facilitate disease therapy.

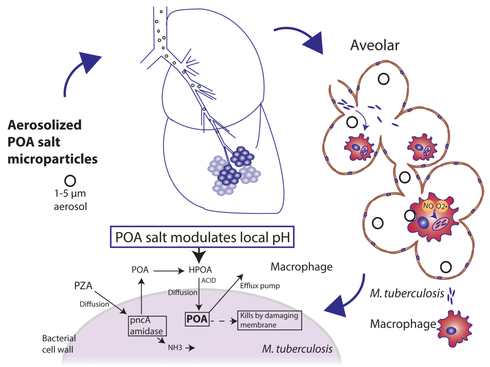


**Figure 1. Pulmonary Administration of POA Salts**

## METHODS

The salts POA-leucine (POA-Leu) and POA-$NH_4$ were prepared. 10 mg/mL aqueous solutions were spray dried (Buchi B-290). Suspensions were atomized using a two-fluid nozzle (liquid inner ⌀ = 0.7mm, gas inner ⌀ = 1.5mm), fed at 6-7 mL per minute. Atomizing gas (ultra high purity $N_2$) was set to a flow rate of 7.3 liters per minute. Drying gas flow rate was maintained at 35 $m^3$/hr. Inlet temperatures was evaluated from 140-190°C, resulting in outlet temperatures ranging from 80-110°C.

Aerodynamic particle size distribution was determined by cascade impaction (Next Generation Impactor, operated at 60L/min) emitted from a capsule based dry powder inhaler (Aerolizer®) and by time-of-flight analysis (TSI Aerosizer).

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.

## RESULTS

Large porous, low density particles of both salts were observed by scanning electron microscopy (FEI Quanta 200). The POA-Leu particles were collapsed hollow spheres with smooth surfaces and small pores. POA-$NH_4$ particles were mostly spherical with a corrugated surface, with an incidence of 15% cubic particles by number. The geometric mean diameters (GMD) were 3.7 and 4.6 µm for POA-Leu and POA-$NH_4$, respectively, as determined by image analysis (n=100).

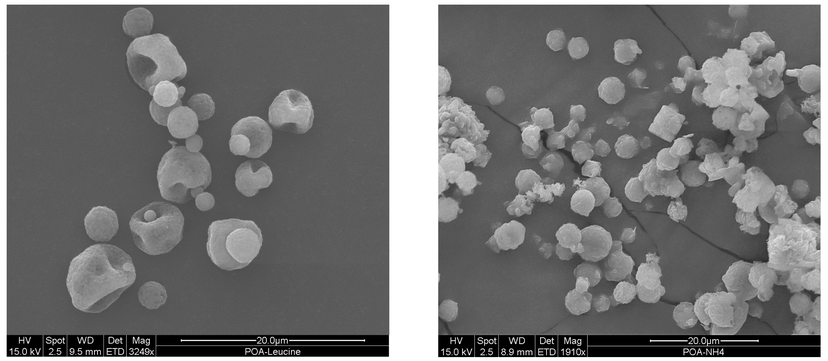


**Figure 2. Spray dried POA-Leucine particles (left) and POA-$NH_4$ particles (right)**

POA-Leu 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-$NH_4$ particles prepared under the same conditions exhibited a MMAD of 5.4 µm (GSD 1.83) and computationally derived FPF(4.46) of 40.%. ED was 81% and 70% for POA-Leu and POA-$NH_4$, respectively.

| Salt | MMAD | GSD | FPF | GMD | ED |
|---|---|---|---|---|---|
| POA-Leu | 1.3* | 1.75* | 29.7% | 3.7 | 81% |
| POA-$NH_4$ | 5.4 | 1.83 | 41% | 4.6 | 70% |

**Table 1. Aerodynamic properties of spray dried POA salts. *Fine mode**

## DISCUSSION

POA-Leu and POA-$NH_4$ compounds were sufficiently soluble to facilitate aqueous preparation. Both salts evaluated resulted in particles with significant mass portion in the respirable size range. The emitted doses for each salt were acceptable.

Morphologically, the POA-Leu particles resemble previously reported particles with moderate leucine content, possibly due to high initial droplet surface saturation during drying.[3] This results in earlier shell formation and larger, less dense particles. Such particles generally are more dispersible than smaller, denser particles. Considering the molecular weights of POA (124.1 g/mol) and leucine (131.17 g/mol), particles prepared using this salt would require larger powder dose to deliver therapeutic doses.

## DISCUSSION CONT.

POA-$NH_4$ particles had an observed small proportion of cubic particles. Differences in particle morphology suggest a need to improve the process. Further optimization of spray drying parameters are required to achieve a homogeneous amorphous product.

POA-$NH_4$ particles also had an aerodynamic diameter that was greater than their geometric diameter. Given the apparent low primary particle density, this suggests insufficient deaggregation.

POA-Leu particles had a higher emitted dose than particles prepared from the POA-$NH_4$ salt. This is likely due to the higher dispersibility of large, low density particles.

## CONCLUSIONS

Both investigated POA salts were suitable for spray drying and their morphology and particle size was within the range suitable for pulmonary delivery.

POA salt excipient selection impacts particle morphology for the same process conditions, potentially influencing aerosol performance.

Further work is required to optimize aerosol dispersion to achieve a unimodal aerodynamic particle size distribution and increase the fine particle fraction.

## ACKNOWLEDGEMENTS

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