ORT_08 - Synthesis of polymeric nanoparticles of a high potency second generation isoniazid derivative aiming tuberculosis treatment via direct delivery to the lung

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Introduction: Tuberculosis (TB) is one of the top ten leading causes of death in medium and low income countries and Brazil one of the nations most affected by this disease. Its treatment is long and full of adverse effects, being isoniazid (INH), one of the drugs of chemotherapy, used in acute and maintenance phases of active TB and in latent TB. However, isoniazid has several drawbacks such as metabolic inactivation, reaction with rifampicin, high hepatotoxicity and there are several *M. tuberculosis* strains resistant to this drug. For such reasons we developed a second generation of INH derivatives bearing a subunit capable of circumventing the main associated INH drawbacks and increasing their *in vitro* and *in vivo* potencies, which is in the oral pre-clinical development phase. Parallelly, the pulmonary administration of the drug encapsulated in polymeric nanoparticles is an option to direct delivery to the lung, increasing the effectiveness of the drug, with a reduction in the frequency of administration due to slower release, bioavailability, and side effects reduction.

Objectives: This work aims to synthesize polymeric nanoparticles of a high potency second generation isoniazid derivative aiming tuberculosis treatment via direct delivery to the lung.

Methodology: The polymeric nanoparticles (PNPs) production process was made by the single emulsion method in organic medium and vacuum evaporation. The organic phase containing the polymer and the isoniazid- analogue (previously dissolved in methanol) was poured into PVA solution and sonicated in ice bath. The emulsion was evaporated under vacuum. Mean diameter, polydispersity index (PDI) and zeta potential were measured by Zetasizer Ultra™. The amount of free isoniazid-analogue was quantified by reverse phase HPLC. Hence the amount encapsulated could be calculated.

Results: The isoniazid-analogue was encapsulated with 86,4% encapsulation efficiency and 16,7% loading capacity. The diameter, PdI and zetapotential were measured as 213,3 nm, 0,03 and -2,8 mv.

Conclusion: The nanoparticles diameter is adequate to target lungs and amount encapsulated shows an efficient encapsulation procedure.

Keywords: tuberculosis, isoniazid, treatment, polymeric nanoparticles