Inhalable Microparticles Embedding Therapeutic CaP Nanoparticles for Heart Target

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Introduction: The aim of this work was to develop an innovative nanomedicine consisting in highly respirable microparticulate dry powder (dpCaPs) able to embed and release Calcium Phosphate nanoparticles (CaPs) loaded with Mimetic Peptide, a therapeutic substance restoring cardiac function. The embedded therapeutic nanoparticles, released in deep lung by carrier dissolution upon inhalation, can target the hearth by translocation to pulmonary vein blood.

Methods: Spray drying technique (SD) was employed to transform the nanoparticle dispersion in inhalable microparticles. Mannitol as water soluble carrier excipient, was used for microparticle construction. *In vitro* respirability was performed using medium resistance Nemera prototype device. Immortalized human alveolar cells and macrophages were exposed to increasing concentrations of microparticles for toxicology investigation. The dry powder formulation was *in vivo* administered to heart diseased mini pig.

Results: The powder having the ratio CaPs/mannitol 1:4 exhibited the best aerodynamic performance for CaP lung deposition and release (CaPs size 85.4 nm). The EF was >92% and the FPF >80%. Microparticles had a spherical shape, rough surface and very low density. The high Extra-FPF (<2µm) favors the CaP deep lung deposition and translocation to the hearth. In vitro evaluation found that dpCaPs were not toxic for human lung alveolar epithelial cells and macrophages and did not induce cytokine release. Finally, the dpCaPs pulmonary administered to diseased mini pigs were able to restore the normal heart contractility.

Conclusion: Highly respirable microparticles able to deliver CaP nanoparticles loaded with Mimetic Peptide from lung directly to the diseased heart were developed.