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Dexamethasone nano-embedded sodium hyaluronate microparticles for treatment of COVID-19 acute respiratory distress syndrome

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Dexamethasone (DX) is a synthetic glucocorticoid employed in a wide range of diseases as immunosuppressant. Recent studies reported that DX could be administered orally or intravenously for the treatment of acute respiratory distress syndrome in patients with COVID-19 phase-3 infection caused by an overreaction of their immune system, reducing 28-day mortality in patients mechanically ventilated or receiving oxygen [1]. Nevertheless, the long-term systemic administration of dexamethasone led to severe side effects, highlighting the urgent need of new strategies for its delivery [2][3]. The aim of this work was to develop a new formulation for inhalation based on DX-nanoparticles. High molecular weight sodium hyaluronate (HA, 750 kDa) was employed to coat DX nanoparticles to exploit HA targeting to CD44 receptors on pulmonary macrophages and its anti-inflammatory effects [4]. DX-nanoparticles were obtained by anti-solvent precipitation using water as anti-solvent dripped into an alcoholic solution of drug. The suspension was spray-dried to obtain a dry powder. Size distribution and morphology of microparticles were investigated by laser diffraction and scanning electron microscopy. Nanoparticle characteristics and composition were assessed after powder redispersion in physiological medium by dynamic light scattering and X-ray scattering techniques. Results revealed the release of quite polydisperse nanoparticles (PdI = 0.3-0.4) with size around 290 nm in water and 180 nm in phosphate buffer. SAXS results showed nanoparticles with a DX-rich crystalline core stabilized in solution by the presence of a shell of HA chains partially embedded in the core. After particle redispersion in water the aerodynamic behavior of the obtained suspension was assessed *in vitro* using a device for aerosol therapy obtaining a Fine Particle Fraction of 87.5 $\pm$ 0.7% while the Emitted Fraction was 26.4 $\pm$ 2.9%. The latter figure represents a limit that may be overcome by nebulizing directly the nanosuspension in the pipe of a ventilator.

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[3] H. Lee, S. W. Jeong, E. Jung, and D. Lee, *Nanomedicine Nanotechnol, Biol and Med.*, **2020**, *30*
[4] J. E. Rayahin, J. S. Buhrman, Y. Zhang et al, *ACS Biomater. Sci. Eng.* **2015**, *1*, *7*.