Nebulization-friendly nanoemulsion formulation for device-targeted co-delivery of celecoxib and naringin for treatment of lung cancer

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Background: Lung cancer is a principal cause of death worldwide, and its treatment is very challenging. Nanotechnology-based delivery systems have gained much interest in treatment of different cancer types owing to their diverse advantages. Particularly for lung cancer, nebulization offers a promising means of targeting drugs to their site of action in the lung. Therefore, nebulizer-friendly nanoparticles preferably in liquid form need to be explored for this purpose.

Methods: In the present study, oil in water nanoemulsion formulations were prepared by homogenization/solvent evaporation method, co-loaded with celecoxib and naringin, colloidally stabilized by Tween 80 surfactant, and then tested for pulmonary administration using different nebulizer types. The nanoemulsions were characterized by evaluation of their particle size, zeta potential, morphological examination, *in-vitro* release profiles of the loaded drugs, stability upon storage, cytotoxicity on A549 lung cancer cell line, *in-vitro* aerosolization behavior, in addition to *in-vivo* safety and biodistribution studies.

Results: The nanoemulsion formulations demonstrated translucent appearance with particle size ranging from 75 to 106 nm, zeta potential values ranging from -3.42 to -4.86 mV, and controlled *in-vitro* release profiles for both drugs. In addition, the nanoemulsion formulation showed favorable stability profiles (owing to steric stabilization by the surfactant), spherical morphology, and superior cytotoxicity on A549 cells. Aerosolization studies on the selected nanoemulsion formulation revealed its high stability to nebulization process, with the generation of aerosol droplets of small volume median diameter (VMD) and mass median aerodynamic diameter (MMAD) <5 μm. Moreover, it demonstrated considerable safety and bioaccumulation in lung tissues, in addition to accumulation in the brain, liver and bones which are the main organs to which lung cancer metastasizes.

Conclusions: Nanoemulsion was proved to be a promising nebulizable system that can be used for co-loading drugs, which paves the way for its usage for treatment of various pulmonary diseases.