Control release of acyclovir nanocrystals from electrospun nanofibers: comparison of two polymeric matrices

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Acyclovir (ACV) is a guanosine antiviral prodrug most commonly used for the treatment of infections caused by: *Human alphaherpesvirus* (HSV) *1 and 2*; *Human alphaherpesvirus* 3 (VZV) and *Human gammaherpesvirus 4* (EBV) [1]. ACV is phosphorylated by thymidine kinases in infected host cells and converted to di- and triphosphate derivatives. These compounds are responsible for ACV inhibitory effects on DNA polymerase [2]. However, this antiviral drug has several limitations. According to the Biopharmaceutical Classification System, ACV can be classified as a class III or IV drug because of its low permeability and solubility. ACV has low bioavailability and its mean plasma half-life is about 2.5 hours, hence, repeated administration of high doses (200-800 mg, five times a day, for 10 days) is needed for the treatment of HSV infections [3,4].

The objective of this study is to develop a novel system for cutaneous application of ACV that is capable of a controlled release of the drug overcoming the limitations of the conventional topical formulations. This novel system consists on the encapsulation of ACV into different polymeric nanofibers composed either by zein from maize or by polycaprolactone (PCL) that are produced by the electrospinning technique. Nanofibers' composition and preparation methods were optimized for the two polymeric systems tested. Controlled release assays were carried out at physiological conditions (pH 5.5 and 37 ºC) in micellar environment (to mimic the biological interface). Controlled release assays of the formulations, where ACV is in the form of nanocrystals, were compared with the commercial topical formulation (Zovirax® cream). The zein nanofibers presented less resistance and worst mechanical properties (Fig. 1-A) than the PCL nanofibers. For PCL nanofibers, the electrospinning technique proved to be efficient in producing high-loaded ACV nanofibers, very resistant and elastic (Fig. 1-B), being a promising approach to reach a sustained drug release profile.

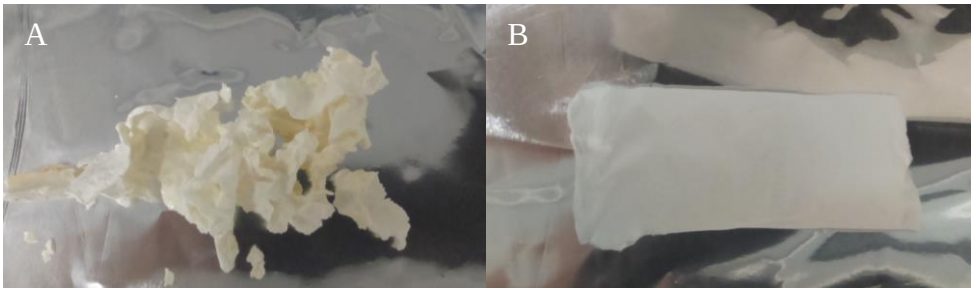

Fig. 1 ACV-loaded nanofibers produced by electrospinning of different polymers: (A) zein from maize and (B) PCL.

As the system that presented the best properties was the one obtained from PCL matrices it was the chosen to proceed with the characterization. PCL nanofibers loaded with ACV were characterized by Scanning Electron Microscopy with Energy-Dispersive X-ray Spectroscopy (SEM-EDS) for topographic and elemental analysis. X-ray diffraction was also used for structural characterization purposes. Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR) was used to characterize the interaction established between ACV and the polymer. Differential scanning calorimetry (DSC) was performed to evaluate the effect of ACV on the polymeric thermal transitions. Cellular viability (MTT assay) was also assessed using HaCaT human epidermal keratinocytes and HFF-1 human foreskin fibroblasts to infer about the ACV-loaded nanofibers' biocompatibility.

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