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Ocular biocompatibility of novel Cyclosporin A formulations based on methoxy poly(ethylene glycol)-hexylsubstituted poly(lactide) micelle carriers.

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Abstract

Topical ocular drug delivery has always been a challenge for pharmaceutical technology scientists. In the last two decades, many nano-systems have been studied to find ways to overcome the typical problems of topical ocular therapy, such as difficult corneal penetration and poor drug availability. In this study, methoxy poly(ethylene glycol)-hexylsubstituted poly(lactides) (MPEG-hexPLA) micelle formulations, which are promising nanocarriers for poorly water soluble drugs, were investigated for the delivery of Cyclosporin A (CsA) to the eye. As a new possible pharmaceutical excipient, the ocular compatibility of MPEG-hexPLA micelle formulations was evaluated. An in vitro biocompatibility assessment on human corneal epithelial cells was carried out using different tests. Cytotoxicity was studied by using the [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] (MTT), and clonogenic tests and revealed that the CsA formulations and copolymer solutions were not toxic. After incubation with MPEG-hexPLA micelle formulations, the activation of caspase-dependent and -independent apoptosis as well as autophagy was evaluated using immunohistochemistry by analyzing the localization of four antibodies: (1) anti-caspase 3; (2) anti-apoptotic inducing factor (AIF); (3) anti-IL-Dnase II and (4) anti-microtubule-associated protein 1 light chain 3 (LC3). No apoptosis was induced when the cells were treated with the micelle solutions that were either unloaded or loaded with CsA. The ocular tolerance was assessed in vivo on rabbit eyes by Confocal Laser Scanning Ophthalmoscopy (CLSO), and very good tolerability was seen. The observed corneal surface was comparable to a control surface that was treated with a 0.9% NaCl solution. In conclusion, these results demonstrate that MPEG-hexPLA micelles are promising drug carriers for ocular diseases involving the activation of cytokines, such as dry eye syndrome and autoimmune uveitis, or for the prevention of corneal graft rejection.

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