Biodegradable polymeric nanoparticles modified with cell penetrating peptides as an effective ocular drug delivery system

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Abstract

The bioavailability of ophthalmic drugs in aqueous solutions is usually low due to their rapid elimination after mucosal instillation; a consequence of reflex blinking and tear drainage, as well as of the presence of the corneal barrier. In fact, only 5% of the applied dose reaches intraocular tissues after corneal penetration [1]. Research into biomaterials has therefore included the use of biodegradable polymeric nanoparticles (NPs) in ocular drug delivery; one of the most promising applications of NPs, as they offer a controlled release profile of a drug which is entrapped in the polymeric matrix [2,3]. These are advantages that suggest that the required therapeutic effects could easily be achieved [4]. Over the years, the potential of a variety of synthetic biodegradable polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymer, poly(lactic-co-glycolic acid) (PLGA), for the production of NPs has been extensively explored due to their biocompatibility, biodegradability and mechanical strength [5]. On the other hand, flurbiprofen (FB) is a non-steroidal anti-inflammatory drug which has been introduced into ocular therapy recently not only for the management of inflammatory diseases that affect ocular structures, but also for use during eye surgery. FB has previously been formulated in PLGA NPs by Vega et al. [6], who achieved good stability and appropriate physicochemical properties for ocular administration, without causing ocular irritancy at any level. Recently, a novel cell penetrating peptide (CPP) for ocular delivery was reported (peptide for ocular delivery; POD) that is capable of transporting both small and large molecules across the plasma membrane [7].
The main aim of this work is to improve the corneal epithelium penetration of NPs composed of PLGA-PEG by means of conjugating POD, the final objective being to achieve a longer sustained release of FB which has been used as an example of NSAID drug.
The NPs were prepared by the solvent displacement method following two different pathways. One involved preparation of PLGA NPs followed by PEG and peptide conjugation (PLGA-NPs-PEG-peptide); the other involved self-assembly of PLGA-PEG and the PLGA-PEG-peptide copolymer followed by NP formulation. The physicochemical and biopharmaceutical properties of the resulting NPs (morphology, *in vitro* release, cell viability and ocular tolerance) were studied. *In vivo* anti-inflammatory efficacy was assessed in rabbit eye after topical instillation of sodium arachidonate. PLGA-PEG-POD-NPs exhibited suitable entrapment efficiency and sustained release. The positive charge on the surface of these NPs, due to the conjugation with the positively charged peptide, facilitated penetration into the corneal epithelium resulting in more effective prevention of ocular inflammation. The *in vitro* toxicity of the NPs developed was very low; no ocular irritation *in vitro (*HET-CAM*)* or *in vivo* (Draize test) was detected. Taken together, these data demonstrate that PLGA-PEG-POD-NPs are promising vehicles for ocular drug delivery.

References

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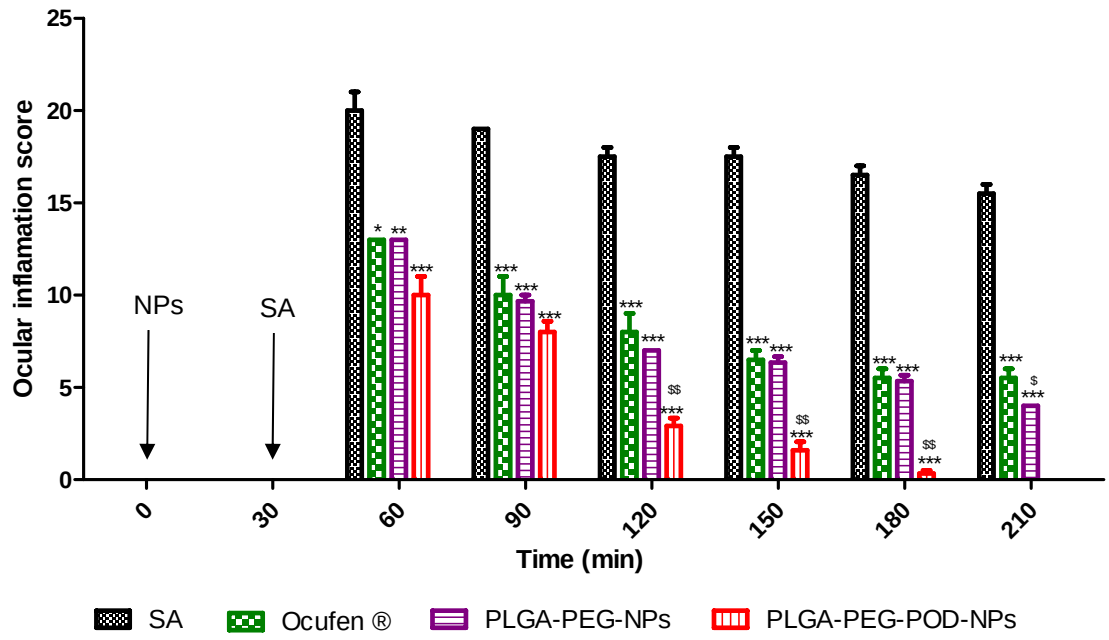
Figure



Comparison of anti-inflammatory efficacy of PLGA-PEG-NPs, PLGA-PEG-POD-NPs and Ocufen® in the prevention of ocular inflammation induced by SA in the rabbit eye. Values expressed as mean ±SD. *P<0.05, **P<0.01 and ***P<0.001 significantly lower than the inflammatory effect induce by AS. ($^{\$}$P<0.05, $^{\$\$}$P<0.01 and $^{\$\$\$}$P<0.001 significantly lower than anti-inflammatory efficacy of Ocufen®.