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Development and characterization of a solid lipid nanoparticle-loaded thermosensitive gel for the delivery of timolol to the eye

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The delivery of drugs to the eye is notoriously challenging. This is due to various physiological barriers which prevent the movement of foreign bodies and substances from getting into the eye, such as the cornea and conjunctiva. In addition to this, biomechanical processes such as the blinking reflex and rapid nasolacrimal drainage removes substances from the surfaces of the eye leading to a very short residency time. The first line treatment for most anterior segment conditions of the eye is the daily administration of drops. These solutions are known to have a low bioavailability, leading to frequent dosing schedules which are often not adhered to by patients correctly. This can be highly detrimental, especially in the case of glaucoma, a condition which is known to cause irreversible blindness due to increased intraocular pressure and subsequent optic nerve damage if not treated adequately from the time of diagnosis. In this study, an innovative formulation composed of drug loaded solid lipid nanoparticles embedded within a thermosensitive gel was developed for the topical administration of timolol to the eye. The polymers employed for the gel were hyaluronic acid and methylcellulose, natural polymers which have been used previously in ophthalmic preparations and are known to be mucoadhesive and biocompatible. The choice of these polymers was aimed at increasing the residency time of the formulation at the surface of the eye to allow for better penetration through the layers protecting the eye. This is of particular importance as the current commercially available eye drops are known to be largely removed from the surface of the eye within 30 seconds of administration. The lipids selected were Compritol® 888 ATO and oleic acid, and the solid lipids nanoparticles (SLNs) were formulated using a nanoemulsion method. This method involved the homogenization of a hot lipid phase upon addition to a cold hydrophilic phase, resulting in the formation of SLNs. The formulated solid lipid nanoparticle gel (SLN-G) system was characterized through various techniques including Fourier Transform Infra-Red (FTIR), thermogravimetric (TGA) and differential scanning calorimeter (DCS) analysis. These characterizations showed a system in which the drug, timolol, was effectively incorporated into the SLN with an encapsulation efficiency of 97.18% and a drug loading capacity of 56.12%. This encapsulation efficiency was further highlighted in the thermal analysis of the SLN-G, TGA and DSC, where the graphs of the drug loaded SLN-G did not show the characteristic peaks of timolol thereby confirming that it was effectively incorporated into the system. Results of the rheology studies revealed that the gel underwent the sol-gel transition at 33 °C when not nano-enabled and at 28 °C when embedded with the SLNs. These are appropriate temperatures for application at the surface of the eye. The average size of the SLNs was 54.75nm and they were spherical in morphology, as confirmed through scanning electron microscopy (SEM) imaging. In addition to this, the in vitro drug release showed an extended drug release profile of approximately 24 hours in comparison to the commercially available product, which releases the drug instantaneously, and could potentially be administered once daily. The current first line glaucoma treatment, timolol eye drops are administered twice daily. By decreasing the frequency of the dosing schedule, patient compliance increases. The SLN-G and its components were also tested for biocompatibility using two different cell lines, Caco-2 and Human Retinal Pigment Epithelial (HRPE) cells. The cell viability was shown to be above 76% for the HRPE after 48 hours of exposure to the drug-loaded SLN-G and above 86% for the Caco-2 cell line, highlighting that the biocompatibility of the formulation. Through these results, it is proposed that an effective alternative to eye drops was developed. The resulting SLN-G illustrates an exciting development in the realm of ophthalmic drug delivery. The primary future prospect of this study would be through further testing in an animal model and, if successful, in a clinical trial model in order for the formulation to be made available on the commercial market. The limitations of the further development would largely be dependent on financial backing. However, due to the extensive positive impact this formulation would have on the quality of the lives of so many people around the world, the effort and financing of future developments would be well worth it.