In situ-forming hydrogel for drug delivery to the posterior eye segment

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Background: Several challenges hinder effective drug delivery to the posterior segment of the eye, including rapid clearance and enzymatic degradation which result in low bioavailability and the need for frequent administration. Intravitreal injections of active pharmaceutical ingredients (APIs) are commonly used to treat posterior eye diseases; however, they can lead to serious adverse effects, the incidence of which increases with dosing frequency. Injectable in situ gelling systems, which undergo a sol-gel phase transition around physiological temperature, offer a promising solution to these issues. The aim of this proposal was to develop an injectable, thermosensitive hydrogel for the sustained release of drugs to the posterior segment of the eye, with the goal of reducing the frequency of administration and, consequently, minimizing the risk of side effects

Methods: Three hydrogels (namely P3/0.1, P3/1, and P4/0.1) were prepared by dissolving and mixing the poloxamers (F127 and F68) with hyaluronic acid (HA) in filtered water at 4°C. Fourier transform infrared spectroscopy (FTIR) was performed on the raw materials and freeze-dried hydrogels to confirm polymer blending. The morphology of the hydrogels was examined using a Field Emission Scanning Electron Microscope (SEM) equipped with an Energy Dispersive Spectrometer. The viscoelastic properties of the hydrogels were evaluated in small-amplitude oscillatory shear experiments using a rotational rheometer, at 4, 25 and 37 °C. Stability at 37 °C was assessed over time intervals of 7, 14, 21 and 28 days. The gelation temperature was identified by monitoring changes in the viscoelastic moduli as the temperature increased from 4 to 45°C, at a controlled heating rate of 1°C/min. Thermodynamic interactions between water and P/HA gels were investigated using a differential scanning calorimeter (DSC), while thermogravimetric analysis (TGA) was employed to evaluate the thermal stability of the hydrogels.

Results: The hydrogels exhibited the rheological behavior typical of a viscous fluid at temperatures below 37°C, transitioning to a gel-like state at physiological temperatures. Stability studies at 37°C demonstrated that the rheological behavior of all hydrogels remained constant over time. Consequently, the platforms retained their stability for up to 28 days when stored at 4°C. SEM micrographs revealed a well-defined network structure with an ordered arrangement, confirming the formation of a self-assembling hydrogel, as further supported by FTIR data. Furthermore, DSC results indicated that incorporation of HA hinders the interactions between water molecules and poloxamers, while TGA outcomes revealed that the presence of HA enhances the thermal stability of the gels.

Conclusions: In this study we developed thermosensitive polymeric platforms by blending poloxamers (F68 and F127) with hyaluronic acid (HA). SEM analyses showed the significant influence of poloxamer and HA on hydrogel structure, while thermal experiments confirmed the role of HA in inhibiting interaction between poloxamers and water. Among the tested formulations, the P3/1 gel emerged as the most promising for ocular drug delivery. In conclusion, these gels show potential for localized ocular delivery by enhancing bioavailability and reducing the frequency of administration. Future studies may focus on incorporating nanoparticles into the hydrogel to develop a composite system capable of further improving and sustaining the release of APIs.