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Development & characterization of injectable depot forming thermoresponsive hydrogel for sustained intrascleral delivery of Sunitinib

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SUMMARY

Age-related macular degeneration (AMD) is a potentially blinding posterior segment disease; inflammatory responses and subretinal drusen formation lead to leaky blood vessels. The current treatment method involves intravitreal injections of anti-VEGF agents, which is highly invasive and requires frequent injections administered by trained personnel. Periocular injections such as trans-/intra-scleral injections would provide a minimally invasive treatment option. The sclera is the outermost protective layer occupying 5/6th of the ocular globe. Owing to its avascular nature and self-healing ability, sclera could be the potential space for the delivery of depot forming long-acting formulations. This project focuses on the development of chitosan grafted poly(n-isopropylacrylamide) (Cs-g-PNIPAAm) gel for the sustained intrascleral delivery of small molecular weight, multiple tyrosine kinase inhibitor Sunitinib malate.

INTRODUCTION

AMD is a multifaceted disorder involving subretinal angiogenesis due to oxidative stress, traumatic injury, and inflammation. Neovascularisation in AMD originates at the choriocapillaris, leading to subretinal haemorrhage and fibrosis. Thermoresponsive *in situ* forming hydrogels are popular among other smart hydrogels as they can form implant/medical devices at body temperature. Poly N-isopropyl acrylamide (PNIPAAm) is a thermoresponsive polymer with a lower critical solution temperature (LCST) of >32°C. PNIPAAm based hydrogels can form hydrophobic interactions with increasing temperature, i.e., at its LCST, water is expelled from the polymer's hydrophilic region, hence trapping the drug, and leading to sustained release.

This study focuses on developing chitosan grafted PNIPAAm (Cs-g-PNIPAAm) hydrogels for the controlled release of SUN, for the efficient treatment of wet AMD. A systematic investigation is undertaken to deliver SUN and Cs-g-PNIPAAm as a drug delivery vehicle for its potential application in treating AMD. Cs-g-PNIPAAm hydrogels were investigated for their *in vitro* drug release, swellability, syringeability, morphology, degradation, stability, and biocompatibility.

MATERIALS AND METHODS

Cs-g-PNIPAAm hydrogel was prepared using free radical polymerization with varying concentrations of chitosan (varying with 10%, 30%, 50% weight percentages) with respect to PNIPAAm. The hydrogels were characterized for rheology, LCST

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measurements, swelling studies, degradation, syringeability, drug release and permeation using Franz diffusion studies. Biocompatibility study of hydrogel was performed with ARPE-19 cells, ocular irritation using HET-CAM test, Further, choroidal angiogenesis was tested on CAM assay and rat choroidal exoplants.

RESULTS AND DISCUSSION

Chitosan grafting was found to have effect on rheological properties of hydrogel and hence on syringeability of formulations. However, chitosan grafting did not significantly affect the LCST of hydrogels, all the formulations exhibited LCST of 32 ± 0.5 °C. 20 µl of 30% Cs-g-PNIPAAm hydrogel was able to release approximately 10 µg/day sunitinib concentration in-vitro for 28 days. It was observed that the drug release from the hydrogel was controlled by both the diffusion and erosion mechanism. Further, the ex-vivo permeation studies on porcine sclera showed that up to 40% sustained release of sunitinib was obtained from hydrogel compared to sunitinib solution (2mg/ml). The optimised formulation (F8) was found to be biocompatible on ARPE-19 cells and no ocular irritation was observed on HET-CAM (Hen's egg test-Choriallantoic membrane) assay. Further, the anti-angiogenic efficacy was conformed using CAM assay and rat-choroidal angiogenesis assay. Wherein F8 hydrogel was found to prevent formation of new blood capillaries compared to control medium.

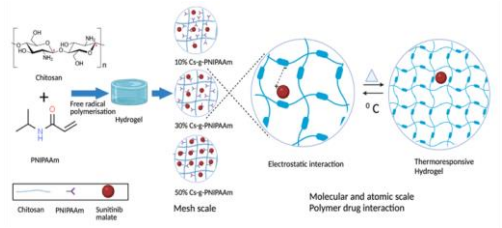

Fig. 1. *schematic representation of mechanism of drug release from Cs-g-PNIPAAm thermoresponsive hydrogel*

Chitosan grafted poly-N-isopropylacryl amide (Cs-g-PNIPAAm) was synthesised with 10, 30, and 50% w/w of chitosan (Cs) to PNIPAAm, by a free radical polymerisation reaction. A weighed quantity of NIPAAm was added to 1% w/v of Cs in acetic acid solution (0.1% v/v). The solution was purged with dry nitrogen for 60 min before polymerisation to remove any dissolved oxygen, to avoid any reaction with free radicals. A 0.131 mmol concentration of the initiator, APS and 0.2 mmol concentration of the accelerator, TEMED, were added subsequently.

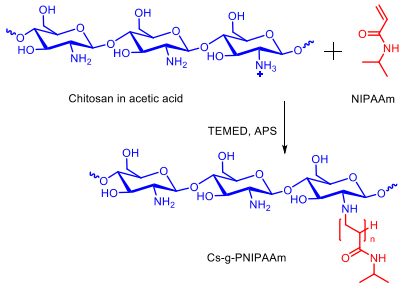

Fig. 2. *Schematic representation of grafting of PNIPAAm with chitosan.*

CONCLUSIONS

The F8 hydrogel was found to be injectable using ultra-thin walled 27G needles. OCT micrographs shows that the F8 hydrogel is able to form depot on-intrascleral injections. Further, dual control over the drug release i.e. temperature controlled gelation and ionic conjugation of sunitinib with amine group of chitosan gives better control over drug release. Hence, Cs-g-PNIPAAm hydrogel would be a minimally invasive sustained release drug delivery alternative to intravitreal injections for the management of AMD.

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