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

Shilpkala Gade[1], Eneko Larraneta[1], Ryan F. Donnelly[1], Rocio Herrero Vanrell[2], Carmen Alvarez-Lorenzo[3], Raghu Raj Singh Thakur[1]

[1]School of Pharmacy, Queen's University Belfast, BT9 7BL, United kingdom; [2]Universidad Complutense de Madrid, Facultad de farmacia, Departmento de Farmacia Galenica y Technologia Alimmentatia, 28040, Madrid, Spain; [3]Departamento de Farmacia y Tecnologia Farmaceutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

Background: 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.

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 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: Chitosan grafting affected rheological properties of the hydrogels and hence on syringeability of formulations. However, chitosan grafting did not significantly affect the LCST of hydrogels, all the formulations exhibited LCST of 32 $\pm$ 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 over 24hrs. The optimised formulation 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.

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