Cytocompatible Nanogels for Sustained Drug Delivery across Ocular Biological Barriers

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Statement of Purpose: Efficacy of ocular therapeutics is limited by ocular biological barriers. Polymeric nanogels and nanoparticles possess high surface to volume ratio and have close interaction between the surface and cells. Nanogels with chemically crosslinked structure can load drugs efficiently and modulate drug release kinetics. The present study aims at developing degradable nanogels to cross ocular biological barriers with enhanced permeability for controlled release of therapeutics to the eye.

Methods: Nanogels, consisted of N-isopropylacrylamide and 2-hydroxyl methacrylate-lactide-dextran macromer, weresynthesized in aqueous medium using UV photopolymerization under stirring. The size and morphology of the nanogels were studied by dynamic light scattering (DLS) and atomic force microscopy (AFM). Fluorescentlabeled insulin was loaded during the synthesis process and released from a 2 mg/mL solution in phosphate buffered saline (PBS, pH 7.4) at 37 °C. Cytotoxicity of the nanogels to R28, ARPE-19 retinal and bovine brain micro vascular endothelial (BBMVE) cells was studied by a MTT cell viability assay. Permeability of the 100 µg/mL nanogels across the ARPE-19 monolayers was measured. Fluorescent-labeled nanogels were administered intravitreally, intravenously, subconjunctivally, and topically to Sprague-Dawley rats and their distribution in the cornea, lens, retina, and vitreous was assessed1day later

Results: DLS and AFM data revealed that the size of the nanogels was around 70-90 nm. Nanogles released FITC-labeled insulin for 2 days in PBS at 37 °C. Up to 1mg/mL concentration of nanogels did not show any cytotoxicity to the R28, ARPE-19, and BBMVE cells (Fig.1)

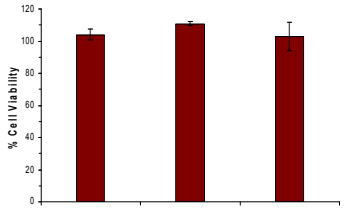

Fig.1. Retinal precursor, R28, adult retinal pigmented epithelial, ARPE-19, and bovine brain microvascular endothelial, BBMVE, cells were incubated with 500 µg/mL of 4:5 nanogels for 1d (2d for R28 cells). MTT assay was used for cell viability studies.

The nanogels were 10 folds more permeable than 4kDa dextran across the ARPE-19 monolayers (Fig.2).

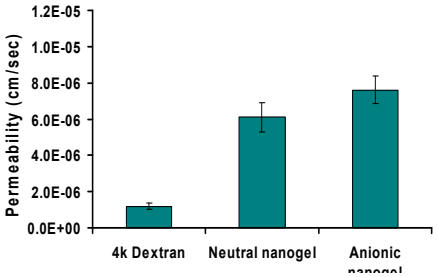

Fig.2. Permeability of 100 µg/mL nanogels across ARPE-19 cell monolayers.

The fluorescent-labeled nanogels were detected in the cornea and retina after intravitreal and subconjunctival injection (Fig.3).

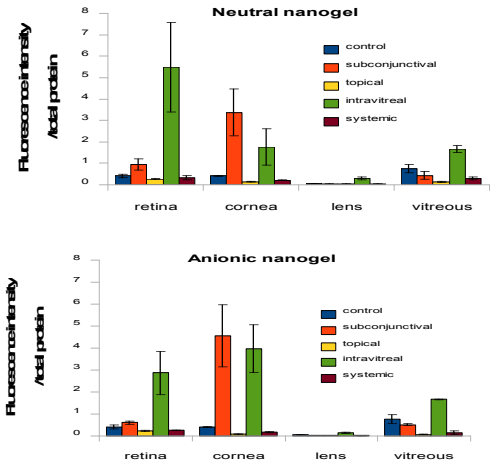

Fig.3. Ocular distribution of DTAF-labeled nanogels. Anionic nanogels contained acrylic acid (10 mole% feeding of NIPPAm and macromer).

Conclusions: The developed non-toxic nanogels are internalized by the retinal precursor, retinal pigmented epithelial, and model microvascular endothelial cells. The nanogels are highly permeable across the ARPE-19 cell monolayers and can reach the cornea and retina strongly after subconjunctival and intravitreal injections. The nanogels have potential to cross the ocular biological barriers and to achieve sustain release of therapeutics to treat ocular diseases.