The development of an *in situ* forming dexamethasone implant to treat diabetic retinopathy

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Background: Intraocular drug delivery devices are a useful way of reducing costs in the long term and improving patient outcomes through the reduction of complications**.** Drug release is an important property that could have an impact on the efficacy of the treatment. This project seeks to develop an injectable implant into the vitreous of the eye that undergoes physical transition upon contact with a physiologically relevant environment. An injectable implant that solidifies upon contact with the vitreous to form a nanocomposite is a useful alternative to current treatments in the market which in some cases involve invasive surgical intervention for insertion. The study aimed to test the hypothesis that drug release can be controlled by using a nanocomposite consisting of an n-isopropylacrylamide (NIPAm) nanogel and a dexamethasone solid drug nanoparticle.

Methods: NIPAm nanogels were synthesized using the dispersion polymerization technique and then combined with the solid drug nanoparticles to create a nanocomposite material. Nanogels were made at sizes 65 nm, 310 nm and 450 nm. Solid drug nanoparticles (SDNs) of dexamethasone were synthesized using emulsion templated freeze-drying technique and characterized using dynamic light scattering and scanning electron microscopy. Long term dispersion and dry dispersion stability studies were used to narrow down from ten to four dexamethasone SDN formulations. Nanogels were combined with the SDNs or free dexamethasone and then 200 µl of the nanocomposite material was injected into porcine vitreous. The resulting vitreous was placed into a 150 µm mesh bag and submerged in phosphate buffer saline (PBS). Samples were collected over set timepoints by removing all the PBS and then replacing them with fresh PBS. Samples were analyzed through reverse phase high performance liquid chromatography after separating excess polymer and surfactant through solid phase extraction.

Results: Stability studies indicated that four out of ten SDNs met the screening criteria set in terms of size, polydispersity index and dispersion rating. The SDNs of choice were Kollicoat/Tween 20, PVA/Tween 20, PVA/Tween 80 and PVA/Solutol. Scanning electron microscopy indicated that the nanocomposites were all crystalline in nature due to the particles being angular. All control samples with SDN only show high levels of burst release where all the drug is collected by the 5-hour timepoint on Day 0 of the experiment. The PVA/Tween 80 sample showed up to 62.6% drug release when combined with the 65 nm NIPAm nanogel where saturation had not been achieved after five days of collecting samples for analysis. Similarly, the PVA/Tween 20 sample showed up to 176.9% drug release when combined with the 310 nm NIPAm nanogel where again, saturation had not been achieved after five days of sample collection. Based on the data obtained for the 65 nm and 310 nm NIPAm nanogels, the PVA/Tween 20 and PVA/Tween 80 SDNs were also taken forward for testing in the 450 nm NIPAm nanogel however in both cases, all drug had been obtained by the 5-hour timepoint on Day 0.

Conclusions: Not all nanocomposites tested indicate slower drug release, however, the cumulative drug release data indicated that at least two out of four formulations have potential to form a slow releasing *in situ* drug delivery system. Following the preliminary drug release data obtained the formulations will be evaluated further using drug vitreous models.