Development of biodegradable *in-situ* depot forming implants for ocular delivery of biologics

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Background: Age-related macular degeneration (AMD) is the most common disease leading to blindness in people of 50 years and over. Patients with AMD are commonly treated with frequently, invasive intravitreal injections of anti-VEGF drugs every 4-6 weeks The high frequency of the injections substantially increases the chance of significant issues such as endophthalmitis and retinal detachment. Biodegradable *in situ* depot forming implants (ISFIs) offer a potential alternative. These systems are designed to be injected into the vitreous humour using normal procedures where they spontaneously form a solid implant that is immediately photocrosslinked to give it longevity. ISFIs are designed to provide therapeutic levels of protein release for several months to drastically reduce intravitreal injection frequency. In this project formulations were designed to provide long-term drug release of a model protein ovalbumin (OVA), for at least 12 months.

Methods: ISFIs were fabricated by using poly (lactic-co-glycolic acid) (PLGA) which is an FDA approved biodegradable polymer, in addition to a photocrosslinkable polymer. The injectability of ISFIs gels were assessed using texture analysis. Furthermore, drug content analysis was assessed by using micro-BCA, *in vitro* release studies were carried out on OVA-loaded implants fabricated with different PLGA type, injection volumes, photoinitiator type and photocrosslinking times. The OVA release was quantified using size-exclusion chromatography. Bioactivity of the OVA in release samples was assessed by using an Enzyme-Linked Immunosorbent Assay (ELISA). Biodegradation properties of ISFIs was tested under ambient and accelerated conditions in sodium hydroxide, in which certain excipients including trehalose and sodium chloride were added as pore-forming agents in an effort to increase degradation rates.

Results: PLGA-based OVA-loaded ISFIs gel showed good injectability. Increasing the PLGA content or the OVA loading resulted in gels that required higher forces to inject, but all remained below the 15 N threshold. The results of content analysis showed that the recoveries of OVA were all higher than 95%. *In vitro* release experiments showed that higher OVA loadings resulted in higher burst release from the ISFIs in addition to higher daily release rates. The difference in the ratio of lactide and glycolide in PLGA also affects the rate and burst of drug release, with higher lactide content leading to reduced burst release due to its increased hydrophobicity. Moreover, different injection volumes of ISFIs all provided sustained release of OVA for several months. Smaller injection volumes lead to ISFIs that were faster to photocrosslink with lower burst release however, they also had lower daily release rates. ELISA results showed that high OVA stability (>80%) was maintained for the duration of the release period studied for all formulations tested. The results of biodegradation experiments also showed that the system was biodegradable *via* hydrolysis and that the degradation rate could be significantly increased by using certain excipients, with sodium chloride being particularly useful in this regard.

Conclusions: PLGA-based ISFIs have the potential to be an alternative treatment to traditional monthly intravitreal injections. These systems can provide long-term, sustained drug delivery, reducing the required frequency of intravitreal injections drastically. ISFI release properties can be customised by changing the parameters shown above. In the future, biologics will be loaded into these ISFIs to evaluate their release profiles and therapeutic efficacy.