# *In situ* forming photocrosslinkable implants for tailorable, sustained delivery of protein therapeutics to the posterior segment of the eye.

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**Background:** Currently, the primary treatment for age-related macular degeneration (AMD) is intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents, proteins that can bind and block the action of VEGF and the neovascularization and subsequent damage to the macula that occurs as a result. These treatments are administered using conventional hypodermic needles, every 4-8 weeks, which pose a risk of sight-threatening complications such as retinal detachment and endophthalmitis and potentially poor patient compliance. *In situ* forming photocrosslinkable implants could provide a platform for injection of suitable anti-VEGF agents using conventional needles, with the photocrosslinkable implant that is subsequently formed in the vitreous humour providing a sustained-release depot, reducing the frequency of injections and the chance of the associated complications. The release characteristics of these implants can be tailored through modifications of OVA-loading, injection volume and photoinitiator type.

**Methods:** Ovalbumin (OVA) was selected as the model protein due to it having a similar molecular weight to that of ranibizumab (43 kDa vs 48 kDa) and loaded into injectable gels containing a photocrosslinkable polymer and poly-lactic-co-glycolic acid (PLGA). The formulation was optimised to provide a high OVA loading (30% w/w), whilst remaining injectable through standard 27-gauge needles, suitable for intravitreal injection. The injectability of the gels and implant *in vitro* release were determined using texture analysis and size-exclusion chromatography (SEC), respectively.

**Results:** All OVA-loaded injectable gels were injectable through 27-gauge needles, suitable for intravitreal injection. All photocrosslinked implants formed from them were capable of sustaining OVA release for several months. The use of different OVA-loadings leads to significant differences in daily release rate, with release rates after 12 months being 1.28, 2.13 and 11.33 µg/day for 15, 20 and 30% w/w OVA-loadings, respectively. Increasing the gel injection volume from 20 µl to 50 µl resulted in higher daily release rates (11.33 vs 14.46 µg/day) after 12 months. The use of Irgacure 819, due to its much higher activity at the 365 nm curing wavelength, resulted in reduced burst release (8.16 vs 27.17%) and daily release rates (2.74 vs 11.33 µg/day) when compared to Irgacure 2959.

**Conclusions:** All OVA-loaded *in situ* implants were successfully fabricated and were proven to be capable of delivering high levels of protein for several months. The implants were also shown to have a tailorable release profile, by alteration of the OVA loading, injection volume and photoinitiator type. These systems could therefore be a promising novel option for the treatment of retinal diseases, such as AMD, with high tailorability depending on the individual needs of the patient and their disease state. In future work, anti-VEGF agents will be tested with this platform to ascertain its true potential in this area.

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