|  |
| --- |
| **Formulation design and evaluation of in situ forming photocrosslinked implant for intravitreal protein delivery** |
| Ge Jiang, Sangdi Wang, David Waite, Raghu Raj Singh Thakur |
| School of Pharmacy, Queen’s University Belfast, Belfast, United Kingdom |
| **Background:** Therapeutic proteins play an important role in the treatment of posterior ocular diseases. For instance, Ranibizumab is one of the commonly used therapeutic proteins for the treatment of age-related macular degeneration (AMD). Clinically, intravitreal injection is the main administration route of therapeutic proteins to the posterior segment of the eye. To maintain the minimum therapeutic protein concentration, patients may need to accept the injection once a month/two months frequently. Frequent intravitreal injection may induce severe side effects such as retinal detachment, vitreous haemorrhage, choroidal inflammation, and high intraocular pressure, etc. Thus, we are developing an injectable in situ forming photocrosslinked implant (ISFPcl) to achieve sustained release of ovalbumin (a model molecule to ranibizumab) via phase inversion to form a solid drug depot and photocrosslink to control the ovalbumin release rate. |
| **Methods:** The ISFPcl consists of Ovalbumin, biodegradable polymer, photocrosslinkable polymer, photoinitiator and solvent. Ovalbumin was grinded through cryogenic milling method into powder to ensure high loading of ISFPcl. The injectability of ISFPcl was evaluated in terms of viscosity and maximum extrusion force via rheometer and texture analyser respectively. The extrusion speed is 0.1 mm/second, and the extrusion distance is 1 mm (equal to 20 µL). The phase inversion of ISFPcl in phosphate-buffered saline (PBS, pH 7.4) was pictured via charge-coupled device (CCD) camera to confirm whether the depot was formed. The injection of ISFPcl in PBS was processed by texture analyser with the same extrusion settings above. The formed depot was crosslinked in the same PBS and moved to optical microscopy for dimensional measurement. The remaining PBS was collected and analysed by HPLC to assess the ovalbumin release during the entire phase inversion and photocrosslink process. The *in vitro* ovalbumin release of Crosslinked ISFPcl was performed in PBS and the released media on the first day was detected via HPLC to assess the burst release profile of ISFPcl. |
| **Results:** When the composition ratios of ovalbumin, biodegradable polymer and photocrosslinkable polymer were constant, the ISFPcl with 20% (w/w) solvent shows lower viscosity (the apparent viscosity 6368 versus 16213 mPa\*s) and maximum extrusion force (3.24±0.35 versus Not injectable) than that without solvent. The injectable formulations of ISFPcl all can form depots in PBS (pH 7.4). The dimensional parameters (length, width, and height) of crosslinked depots with solvent did not show significant difference to depot without solvent. The ISFPcl with 20% (w/w) solvent releases more than 40% (w/w) ovalbumin during the phase inversion and photocrosslink and after the first day release, more than 50% (w/w) ovalbumin escapes from the ISFPcl matrix, which indicates that it is imperative to regulate the composition ratio of solvent to balance the good injectability and reduced burst release of ovalbumin. |
| **Conclusions:** Compared to the preformed intravitreal implants, the injectable ISFPcl can be easily administrated into vitreous humour through the current intravitreal injection procedure. Also, the sustained release profile can be achieved in the injectable ISFPcl, which will reduce the injection frequency and improve the patient compliance possibly. However, there is still much more work need to be done in the optimisation of ISFPcl formulation composition ratios to achieve the target product profile.  |