Depot Forming Dissolving Microneedle for Intrascleral Protein Delivery

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Background: Age-related macular degeneration (AMD) is a chronic progressing degeneration of the macula and is the leading cause of vision impairment among elderly individuals. Currently, the intravitreal injection of anti-vascular endothelial growth factor (Anti-VEGF) agents is a standard approach for AMD treatment. However, owing to the chronic nature of AMD, patients require frequent injections, performed by highly invasive hypodermal needles. Therefore, the intravitreal route is always associated with severe complications, such as retinal detachment, endophthalmitis, and cataract development. Dissolving microneedles (MNs) have been proposed as an alternative to the hypodermic needle, offering minimum invasion and increased patient compliance. Therefore, in this study, ovalbumin (OVA)-loaded dissolving MNs have been fabricated to transport protein to the back of the eye in a minimally-invasive manner. A number of polymers have been selected and assessed for fabrication of dissolving MNs and assessed for its characteristics to develop optimised delivery system.

Methods: OVA was used as a model protein and four polymers hyaluronic acid (HA), polyvinyl acetate (PVA), polyvinylpyrrolidone (PVP) and the mixture of PVA and PVP were selected for MN preparation. The MN arrays contained 9 (3*3) conical-shaped needles, approximately 700 µm in height, with a base width of 300 µm and 50 µm interspacing were fabricated using MN moulds. MNs were characterised for its morphology, mechanical strength, insertion depth, dissolution time and *in vitro* permeation, followed by a cell toxicity assay in human retinal pigment epithelial (ARPE-19) cells lines.

Results: The results of light microscopy and scanning electron microscopy imaging indicated that all polymers investigated were feasible to be fabricated into MN arrays with sharp needles. Optical coherence tomography showed that except for the OVA MN made of HA, which were too soft to penetrate the porcine sclera, all other MNs prepared from PVA, PVP and their mixtures were successfully inserted into the porcine scleral tissue with insertion depth greater than 75% of the total MN height. OVA MNs fabricated from all selected polymers were found to possess the rapidly enough dissolution (< 3 min) within the scleral tissue. OVA was successfully delivered across porcine sclera *in vitro*, with PVP MN delivering the greatest amounts (i.e. 57.87±2.20 µg) in 24 hours, which was three times higher compared to conventional formulations (e.g. topical eye drops and gels). Furthermore, it was found that the viability of ARPE-19 cells was always >76%, which demonstrated that all selected polymers were non-toxic to retinal cells.

Conclusions: This study optimised the polymer for rapidly dissolving MN applied for posterior segment protein delivery via intrascleral route. Except for the MN composed of HA, MNs fabricated from other polymers were sharp and robust enough to puncture the scleral tissue with limited reduction of height. *In vitro* studies indicated that MN made of all selected polymers could rapidly dissolve within the tissue after insertion and showed an increased degree of permeation of model protein, which demonstrates that dissolving MN is capable of bypassing ocular barriers and delivering high molecular weight proteins in close proximity to the target tissue (choroid/retina). Moreover, the materials used in the fabrication of MNs were found to be biocompatible for human retinal cells. In futures work, OVA-encapsulated nanoparticle will be loaded into dissolving MNs to sustained the release of drugs from rapidly dissolving MNs and ultimately provide a minimally invasive and long-term treatment for the posterior segment of ocular diseases.