Novel electrospun implants of Sunitinib can depress ex-vivo ocular neovascularization

Deepakkumar Mishra[1], Hákon Hrafn Sigurðsson[2], Ana Paula Serro[3],Giedrius Kalesnykas[4], Ryan Donelly[1], Thakur Raghu Raj Singh[1]

[1] School of Pharmacy, Queen's University, Belfast, BT9 7BL, United Kingdom
[2] Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavík, 102, Iceland
[3] Chemical Engineering Department, Instituto Superior Técnico, Lisbon,1049-001, Portugal
[4] Experimentica UAB, Vilnius, 10223, Lithuania.

Background: Current management of posterior segment disease such as Age-related Macular degeneration (AMD) and Diabetic Macular Edema (DME) is by monthly Intravitreal injections of Anti-VEGF agents (IVT). IVT therapy suffers from various serious drawbacks such as highly invasive procedure and risk of ocular tissue damage. Moreover, Lower response rate of Anti-VEGF agents in patients also demands development of novel alternative therapies. One of the major challenge of posterior segment drug delivery is selection of suitable in-vivo models for pharmacokinetic and therapeutic screening due to highly localized nature of eye leading limited choices animals that resemble human ocular anatomy. Hence we aim to novel episcleral implant platform for posterior segment drug delivery along with using suitable ex-vivo assays for therapeutic estimation of developed drug delivery systems.

Methods: The Implants loaded with sunitinib malate were fabricated using a polymeric blend of gelatin and polyglycerol sebacate (PGS) by electrospinning technique. The effect of polymer blending and drug loading on morphology and in-vitro drug release profile by scanning electron microscopy and shaking incubator drug release method. Further, the effect of electrospinning and polymer blending on mucoadhesion was studied by mucin agar plate method. Transscleral drug permeation and the secondary depot formation of sunitinib following episcleral application were studies Franz diffusion cell experiment. The biocompatilbity of implant was tested on ARPE-19 cells and the effect of treatment on cell morphology was studied by crystal violet staining. The therapeutic efficacy of episcleral implants was tested by ex-vivo choroidal angiogenesis assay.

Results: The electrospinning process lead to development of highly porous and flexible implants. It was found that polymer blending has profound effect on the morphology as well as in vitro drug release of implants. The addition of PGS lead to thinner fibres within implant and it also lead to sustained release of sunitinib over the period of one week. The drug loading did not has proficient effect on the morphology of implants however higher loading lead to sustained release of sunitinib over the release period. The electrospinning process lead to enhanced mucoadhesion that could possibly due to increased surface area and improved contact angle. The implants were found to be biocompatible and did not alter the morphology of ARPE-19 cells upon treatment as observed by crystal violet staining. The drug release samples of implants in cell culture media were tested upon ex-vivo rat choroidal angiogenesis assay where it was observed that the release samples were able to suppress the ocular neovascularization significantly when compared with untreated samples.

Conclusions: We can conclude that sunitinib loaded episcleral implants could be a promising alternative for management of disease with posterior segment neovascularization such as AMD and DME. The polymer blending of different polymers along with electrospinning technique could aid in development of novel episcleral implants with sustained release of medicinal agents. The electrospun implant platform could also be used for anterior segment drug delivery as well. Finally ex-vivo rat choroidal angiogenesis assay could be a great tool for therapeutic screening of ocular drug delivery systems