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

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SUMMARY

Choroidal neovascularization (CNV) is one of the hallmark symptoms of Wet Age-related Macular Degeneration (wAMD) and Diabetic Retinopathy(DR) which involves formation of neoangiogenic i.e. formation of new abnormal blood vessels emerging from the choroidal blood vessels and protruding through retinal layer. The current management of wAMD involves intravitreal injections of anti-VEGF such as ranibizumab and aflibercept. We hypothesized the delivery of small molecule anti-angiogenesis agent such as Sunitinib by episcleral route could be an effective and less challenging solution for the management of the choroidal neovascularization. In this research, we have fabricated the sunitinib-loaded implants that are able of sustained release of drug and possess improved ocular pharmacokinetics with a non-invasive administration. The novel episcleral implants were fabricated by electrospinning and were test for different physiochemical and well as *in-vitro* pharmacokinetic properties. Further, these implants were tested for in-vitro biocompatibility and ex-vivo efficacy for estimation of pharmacodynamics properties.

INTRODUCTION

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 challenges 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 develop novel episcleral implant platform for posterior segment drug delivery along with using suitable ex-vivo assays for therapeutic estimation of developed drug delivery systems

MATERIALS AND METHODS

All the chemicals for synthesis were purchased from Sigma Aldrich. The implants loaded with sunitinib malate were fabricated using a polymeric blend of gelatin and PGS by electrospinning technique. The effect of polymer blending and drug loading on morphology and in-vitro drug release profile were studied 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

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cell experiment. The biocompatibility 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.

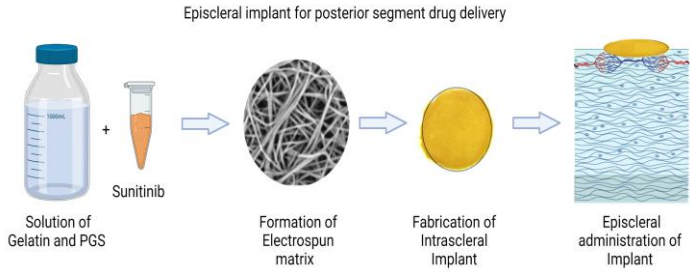

Fig. 1. *Overview of the study*

RESULTS AND DISCUSSION

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. (Table. 1.)

Table 1. *Composition of different episcleral implants fabricated by electrospinning process.*

Name	Polymer blend	Drug concentration (%w/w)	Fibre diameter (µm)
Formulation-1	60%w/w	5	1.82±0.13
Formulation-2	40%w/w	5	2.78±0.38
Formulation-3	20%w/w	5	3.18±0.37
Formulation-4	0%w/w	5	5.80±0.39
Formulation-5	60%w/w	0	1.84±0.12
Formulation-6	60%w/w	10	2.49±0.38
Formulation-7	60%w/w	20	2.48±0.29

The drug loading did not have proficient effect on the morphology of implants however higher loading lead to sustained release of sunitinib over the release period. (fig.1.) the electrospinning process led to enhanced mucoadhesion that could possibly be due to increased surface area and improved contact angle (Fig.2.). 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.

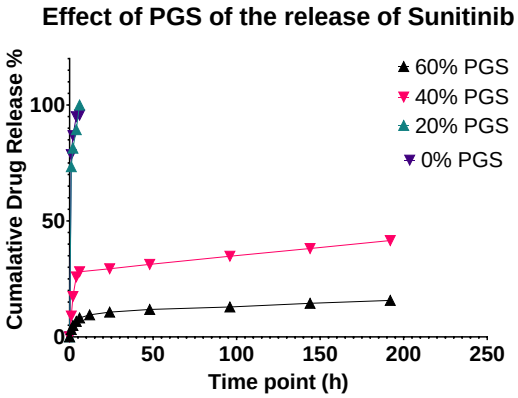

Fig. 2. *Drug release profile comparison different episcleral implants. Higher amount of sunitinib in implant lead to sustained release when compared with lower amounts.*

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.

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