ABSTRACT
Primary intraocular lymphoma (PIOL) is a rare form of lymphoma which is encountered in ocular oncology practice. Most preferred treatment has been intravitreal MTX injections which do not have a long lasting chemotherapeutic effect due to rapid elimination of the drug. In this study, chitosan (CS) and polylactic acid (PLA) based intraocular implants are fabricated for different MTX loadings (10%, 25% and 40% w/w). The implants administer a therapeutic dosage of 0.2-2.0 µg/day of MTX over a period of a month. PLA coated CS-MTX implants can be used for sustained release of MTX, thereby improving the treatment of PIOL.

INTRODUCTION
Primary intraocular lymphoma (PIOL), a non-Hodgkin’s lymphoma (NHL) of B-cell origin is a subset of primary central nervous system lymphoma (PCNSL) (1, 2). At present, the most preferred treatment of PIOL is repeated intravitreal injections of MTX. MTX intravitreal injection has a short half life ($t_{1/2}$) of 14.3 hours and repetitive administrations are required to maintain therapeutic dosage over a period of time (1). In the work of Velez et al. (2), intravitreal injection of methotrexate sodium (400µg) in rabbit eyes was therapeutic (>0.5 µM) for 48-72 hours. Repetitive administrations of injections can also cause local and systemic toxicity.

There is a need for a sustained release drug delivery system to maintain the therapeutic dosage of MTX for a prolonged time. In the study by Palakurthi et al. (1), it was suggested the ideal MTX intravitreal implant would need to administer MTX within the therapeutic window of 0.2-2.0 µg/day for a period of a month or more for improved treatment of PIOL. In this study a CS based MTX intravitreal implant is fabricated to treat PIOL. It has been mentioned by de la Fuente et al., that CS based ocular drug delivery formulations have shown good tolerance in terms of toxicity (3). Also, CS has been used as a delivery vehicle for MTX in other formulations (4). The CS-MTX implant releases MTX rapidly because of hydrophilic nature of both CS and MTX. The CS-MTX implant is therefore coated with a hydrophobic coating of PLA for sustained release of MTX. The hypothesis of this study is that the PLA coated CS-MTX intravitreal implant will administer MTX within the therapeutic window for a period of over one month, thereby enhancing the efficacy of the drug in retarding the progression of PIOL.

Figure 1. A. Top View of PLA coated implant; B. Top View of uncoated implant; C. Cross sectional View of PLA coated implant showing PLA coating on the edge; D. Cross sectional View of uncoated implant. (Scale = 500 µm)
METHODS

MTX is mixed with low molecular weight chitosan in dilute HCl to make different mixtures of 10%, 25% and 40% w/w drug loadings. These mixtures are then injected into Tygon® tubing (1/16 in I.D.) to make different mixtures of 10%, 25% and 40% w/w drug loadings.

MTX is mixed with low molecular weight chitosan in dilute HCl as shown in Figure 2D. The total release duration for 10%, 25% and 40% w/w PLA coated CS-MTX implants is 58, 74 and 66 days respectively shown in Figure 2D. The mean release rate of the coated implants was measured using an UV-Visible Spectrophotometer. The evaluation of the implant dimensions and appearance was conducted using an optical microscope.

RESULTS

Dimensions and Appearance. The optical microscopy images of the PLA coated and uncoated implants showing the dimensions are shown in Figure 1. The images reveal uniform mixture of CS and MTX. A 100 µm PLA coating can be noticed in Figure 1C in PLA coated CS-MTX implant. The length and diameter of the PLA coated implant is 4.2 ± 0.03 mm and 0.90 ± 0.04 mm respectively (Figure 1A). The length and diameter of the uncoated implant is 4 ± 0.04 mm and 0.70 ± 0.03 mm respectively (Figure 1B).

Release rate study of the uncoated implants. The release rate of the uncoated implants is shown in Figure 2A and the release rate of the uncoated implants in the therapeutic window (shaded region) is shown in Figure 2B. The total release duration for 10%, 25% and 40% w/w CS-MTX implants is 20, 30 and 32 hours respectively as shown in Figure 2B. The mean release rate of the coated implants is 88.9 ± 4.8 µg/day, 188.0 ± 7.9 µg/day and 372.6 ± 7.5 µg/day for the 10%, 25% and 40% w/w drug loadings respectively.

Release rate study of the PLA-coated implants. The release rate of the PLA coated implants is shown in Figure 2C and the release rate of the coated implants in the therapeutic window (shaded region) is shown in Figure 2D. The total release duration for 10%, 25% and 40% w/w PLA coated CS-MTX implants is 58, 74 and 66 days respectively as shown in Figure 2D. The mean release rate of the coated implants is 1.8 ± 0.4 µg/day, 3.2 ± 0.1 µg/day and 6.6 ± 0.3 µg/day for the 10%, 25% and 40% w/w drug loadings respectively.

Release Kinetics Analysis. Drug release rate data of all drug loadings of the coated implants were fitted to first order equation. The fitting is evaluated based on correlation co-efficient (R²) values. The R² values range from 0.85 to 0.91, which implies that the drug release rate from the coated implants is dependent on the concentration of the drug in the implant.

CONCLUSION

The uncoated CS-MTX implants are able to administer the drug for around a day. The PLA coated CS-MTX implants are able to administer the drug release for more than 50 days. The hydrophobic PLA coating enables sustained release of MTX. The PLA coated CS-MTX implants can be used for better treatment of PIOL.

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REFERENCES