PLA / PLGA-COATED CHITOSAN MICRO-IMPLANTS FOR SUSTAINED RELEASE OF METHOTREXATE TO TREAT VITREO-RETINAL DISEASES

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INTRODUCTION

At present, Methotrexate (MTX), a hydrophilic antimetabolite chemotherapeutic drug is being used for the management of vitreo-retinal (VR) diseases, such as retinal detachment and proliferative vitreoretinopathy. Serial intravitreal injections containing ~ 400 µg of MTX is being administered in clinical practice, which results in rapid clearance of the hydrophilic MTX with a short half-life of 14.3 hours (1). In order to maintain therapeutic efficacy, repetitive intravitreal injections of MTX are administered, which often results in collateral trauma, complications and ocular toxicity. It is expected that a sustained release drug delivery device (micro-implant), which maintains a therapeutic release rate of 0.2-2.0 µg/day of MTX for a period of a month or more would avoid the possible complications associated with an injection (2).

Currently, no sustained release devices for hydrophilic drugs, such as MTX, in the VR domain have been reported. The challenge to fabricate a sustained release device for hydrophilic drugs is that they do not blend well with existing FDA approved lipophilic materials, such as poly-lactic acid (PLA) and poly-(lactic-co-glycolic) acid (PLGA), which is a copolymer of PLA and poly-glycolic acid (PGA). Due to the similar hydrophilic nature, chitosan (CS), a biocompatible and biodegradable polymer, is used as a matrix to blend MTX. Since both CS and MTX are hydrophilic in nature, MTX is expected to be released rapidly out of the CS-MTX micro-implant. Therefore, a lipophilic surface modification of the CS-MTX micro-implant is required to cause sustained release of MTX.

In a prior study, a PLA-coated CS-MTX micro-implant was fabricated which was able to administer therapeutic release rate of MTX for 56-70 days (3). In this study, PLGA copolymer and PLA has been used for improved control of MTX release rate. The objective of this study is to characterize the influence of a) PLGA:PGA copolymer ratio in PLGA and b) the molecular weight of PLA on the MTX release rate, swelling and structural stability of the micro-implants.

Figure 1: Optical microscopy and SEM images of the top view and the cross-sectional view of the CS-MTX micro-implants coated by PLGA 5050 (A.,B.,C.,D., respectively); PLGA 6535 (E.,F.,G.,H., respectively); PLGA 7525 (I.,J.,K.,L., respectively); PLA 100 (M.,N.,O.,P., respectively); and PLA 250 (Q.,R.,S.,T., respectively)
METHODS

MTX is blended with CS (M.W: 50,000-190,000) in dilute HCl to obtain a mixture containing 40% w/w MTX. The CS-MTX mixture is injected into Tygon tubing (1/16 in. ID) and freeze-dried to obtain CS-MTX fibers, which are cut into desired lengths (~ 4 mm) (3). For lipophilic surface modification, the CS-MTX micro-implants containing ~ 400 μg of MTX, are dip coated with fixed concentrations of different PLGA combinations (PLGA 5050, PLGA 6535 and PLGA 7525, where PLGA - 50:50, 65:35, 75:25, respectively; M.W. 54,400 - 103,000) and PLA combinations (PLA 100 and PLA 250 of MW: 102,000 and 257,000, respectively). Fourier transform infrared spectroscopy (FTIR) are employed to characterize chemical bonding of the coating with the CS-MTX matrix. The comparative assessment of a) the MTX release rate and b) the swelling of the different PLA / PLGA coated CS-MTX micro-implants is conducted to investigate the effect of the lipophilic surface modification on the sustained release of MTX. The MTX release rate study and the swelling analysis are conducted by placing the PLA / PLGA-coated CS-MTX micro-implants (n = 3, for each type of coating) in a vial containing 5 ml of phosphate buffered saline (pH 7.4) in a water bath at 38°C. Samples are assayed at predetermined time intervals for a) MTX release rate using UV-Visible Spectrophotometer (MTX characteristic peak at 258 nm) and b) swelling (% weight difference of the micro-implant.

RESULTS

Morphology and Structure. The length and cross-sectional diameter of the micro-implants are 4.3 mm and 1.2 mm, respectively. The porosity of the micro-implant surface and matrix is reduced with an increase in a) PLA content in PLGA and b) molecular weight of PLA (Fig. 1). FTIR results show the characteristic peaks of CS and MTX (3355 cm⁻¹ and 3284 cm⁻¹ for O-H and N-H stretching) and the peaks of PLGA (2969 cm⁻¹ and 2943 cm⁻¹ for stretching of aliphatic groups; 1741 cm⁻¹ for carbonyl stretching and 1180 cm⁻¹ for C-O stretching) are restored in the PLGA / PLGA coated CS-MTX micro-implant (Fig. 2). This confirms that there is no chemical bonding between the PLA / PLGA coating and the CS-MTX matrix.

MTX Release. The mean release rate of the coated CS-MTX micro-implants is 5.4 ± 0.1 μg/day (PLGA 5050), 5.7 ± 0.5 μg/day (PLGA 6535), 3.4 ± 0.6 μg/day (PLGA 7525), 3.3 ± 0.3 μg/day (PLA 100) and 1.8 ± 0.1 μg/day (PLA 250) (Fig. 3). The total release duration of MTX from the coated CS-MTX micro-implants is 82 days (PLGA 5050), 82 days (PLGA 6535), 138 days (PLGA 7525), 138 days (PLA 100) and 150 days (PLA 250). The half-life (t_{1/2}) of MTX release from the coated micro-implants is 11.3 days (PLGA 5050), 11.8 days (PLGA 6535), 24.9 days (PLGA 7525), 18.6 days (PLA 100) and 100.3 days (PLA 250), when the release data is fitted to the first-order equation.

Swelling Analysis. The peak swelling of the CS-MTX micro-implants coated with PLGA 5050, PLGA 6535, PLGA 7525, PLA 100 and PLA 250 is observed to be 6.2 times (30th day), 7.4 times (82nd day), 6.2 times (114th day), 2.2 times (222nd day) and 2.1 times (229th day), respectively (Fig. 4).

CONCLUSIONS

It is observed that with an increase in a) PLA content in PLGA and b) molecular weight of PLA, the mean release rate of MTX and swelling of the micro-implant reduces, stability improves and the overall release duration of MTX increases. Therefore, the lipophilic surface modification of the CS-MTX micro-implant surface is important for improving and optimizing the release duration of MTX.

REFERENCES


Figure 2: FTIR spectra of CS, MTX, uncoated CS-MTX micro-implant, PLGA/PLA, and PLGA/PLA-coated micro-implant

Figure 3: Release rate profiles of MTX from the PLGA-coated micro-implants and PLGA-coated micro-implants

Figure 4: Swelling profile of the PLGA-coated micro-implants and PLA-coated micro-implants