Bovine Serum Albumin-Meloxicam Nanoaggregates Laden Contact Lenses for Ophthalmic Drug Delivery in Treatment of Postcataract Endophthalmitis

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ABSTRACT SUMMARY
This study dispersed bovine serum albumin-meloxicam nanoaggregates (BSA-MX-NS) in contact lenses to reduce the irritancy of meloxicam to ocular tissues and increased the drug release duration. Results prove that the developed contact lenses loaded with BSA-MX-NS could release drugs for about five days and attenuate the ocular irritancy of drug with improved anti-inflammatory efficacy, offering a useful attempt in postcataract endophthalmitis treatment.

INTRODUCTION
Endophthalmitis is a serious intraocular infection most commonly as a complication of cataract surgery and often causes severe visual impairment or even the loss of an eye. Topically applied nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the treatment of ocular inflammation after cataract surgery. However, such NSAIDs therapy are mostly coupled with severe local discomfort due to their COXs inhibiting nature. Besides, most topical ophthalmic treatment employs eye drops for drug delivery into the lower cul-de-sac, where less than 5% of an applied dose could effectively reaches the intraocular tissue due to corneal barriers. Several researchers have focused on delivering drugs through contact lenses with significantly raised residence time leading to an over 50% bioavailability of drugs² and reduced side effects.

Our focus is to design a contact lens based drug delivery system for poorly soluble drugs meloxicam (MX) offering prolonged drug release, and minimal ocular irritancy in the treatment of entophalmia or inflammation after cataract surgery. Our approach is based on stabilizing meloxicam in aggregates of nanocrystals and dispersing the nanoaggregates in contact lenses. Meloxicam nanocrystals (MX-NS) were further coated by bovine serum albumin (BSA) for the consideration of reducing irritancy of MX and controlling the drug release rates. Additionally, studies show that BSA displays easy accumulation and uptake in inflamed tissues³. We propose a method for preparing nanocrystals without using organic solvents and much surfactants based on the pH-dependent solubility of meloxicam. With all the efforts above, we focus on developing BSA coated MX nanoaggregates incorporated contact lenses as a potent DDS for the treatment of entophalmia after cataract surgery.

EXPERIMENTAL METHODS

The BSA-MX nanoaggregates were prepared as follows: 40 mg meloxicam and 200 mg BSA were dissolved in 4ml NaOH solution, and 150 mg Tween-80 was added into 4 ml HCl solution. The NaOH solution was injected into HCl solution under moderate stirring at 4°C. Additional NaOH solution was added for pH adjustment. The MX-NS-laden p-HEMA gels was synthesized as follows: 5 mL of ophthalmic grade 2-HEMA monomer was mixed with 0.2 mL TEGDMA and added to a solvent mixture of water/ethylene glycol (1.0 mL/1.5 mL). Various amounts of BSA-MX-NS were added to the monomer solution and vortexed prior to adding the catalyst and initiator, 0.5 mL of 15% sodium metabisulfite and 0.5 mL of 40% ammonium persulfate, respectively. The mixture was allowed to polymerize between two glass plates overnight at room temperature. Then the resulting polymer was soaked in deionized water for 4 h before cut into circular piece for use. Images of the surface and section features of the polymer gels were obtained using SEM.

The release of drug from BSA-MX-NS laden p-HEMA gels was measured by soaking the gel in a GBR solution of 200ml with stirring at the speed of 50 rpm at 34°C. The drug concentration in the GBR solution was determined at wavelengths of 362 nm at predetermined points.

The irritancy and efficacy of developed drug loaded contact lenses was performed according to the Draize technique on New Zealand white albino rabbits. Ocular inflammation was elicited by topical administration of 0.5% sodium arachidonate (50 μl). Evaluations were made every 24 hours up to 5 days. The Draize score was determined by visual assessment of changes in these ocular structures. After the irritation examination, rabbits were sacrificed by air embolism, and the eye tissues (cornea, conjunctiva, iris and sclera) were made into histological section for histopathology microscopy.

RESULTS AND DISCUSSION
The developed BSA-MX-NS laden p-HEMA gels releases drugs for about five days in a gel controlling manner (Fig. 1).
The release duration can be affected by gel thickness (data not shown) and cross-linking degree. The SEM pictures of polymer matrix with various cross-linking degree (Fig. 2) can offer a better explanation. The polymers cross-linked with 25μL TEGDMA displays a flat, regular with partly corrugated pattern on surface. When TEGDMA increases to 50μL, the corrugated pattern is spread to all over the gels, and appears larger and deeper. As for the gels with 100μL cross-linkers, the pattern again appears larger and deeper, but no breakage was observed. Finally at 200μL of TEGDMA, the bounded HEMA molecules layers breached on the surfaces and the gaps generate spaces for MX to escape. Therefore, the HEMA on the surfaces can be hypothesized to cross-linked with sub-surface molecules, which react with molecules deeper in the bulk of the polymer, causing disturbance or disrupting effects to the polymer matrix. SEM pictures from the gel sections proved this hypothesis (figure not shown). The polymers with 25μL and 50μL TEGDMA appears similar with flat and regular in its vertical section, but fine for 25μL and rough for 50μL. When the volume of cross-linker increases to 100μL, small bumps were observed in section, and grow larger and more aggregated when the volume of TEGDMA goes 200μL. This further proves that the excessive cross-linker TEGDMA introduces disturbing effect to the polymer matrix.

**Fig. 1** Cumulative release from BSA-MX-NS laden p-HEMA gels with different cross-linking degree.

**Fig. 2** SEM pictures of BSA-MX-NS laden p-HEMA surfaces crosslinked with 25, 50, 100, and 200 μL TEGDMA.

The irritation test showed no signs of severe discomfort in any of the investigated groups (data not shown). The histopathology study (Fig. 3) revealed mild edema in some parts underside the cornea in the group of uncoated MX-NS, illustrating that the BSA coating is effective in reducing the irritancy of MX to the ocular tissue by reducing the drug exposure. Morphologic changes of conjunctival epithelium cells was observed accompanied with slight neutrophils invasion in cellular matrix in MX solution group due to the irritant additives for drug solubilization. The efficacy study showed when MX was loaded in biocompatible p-HEMA gels for precorneal delivery, MX retained in the gels could stay at the ocular surface for longer times and the amount progressively released from them was immediately and completely available for trans-corneal absorption (figure not shown).

**Fig. 3** Histopathology microscopy of the ocular tissues including cornea, conjunctiva and iris after treated with different MX formulations for 5 days.

**CONCLUSION**

The developed BSA-MX-NS loaded in the p-HEMA hydrogel polymer matrix released drugs over 5 days. The release duration can be affected by the gel thickness and the cross-linking degree. Excessive cross-linkers bring larger crevices on the surface and larger bumps in the sections leading to fast drug release. BSA-MX-NS loaded p-HEMA gels is significantly less irritating to the ocular tissues as compared to marketed MX solutions in the irritation test carried out on rabbit eyes and showed a prominent response in reducing ocular inflammatory.

**REFERENCES**