Hydrogel Containing Silica Shell Cross-linked Micelles for Ocular Drug Delivery

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ABSTRACT: Poly(2-hydroxyethyl methacrylate–methacrylic acid–ethylene glycol dimethacrylate) hydrogels loaded with silica shell cross-linked methoxy(polyethylene glycol)-*block*-polycaprolactone (MePEG-*b*-PCL) micelles with rod-like morphology were prepared as a potential soft contact lens material for the sustained release of ocular drugs. The silica shell cross-linked methoxy micelles (SSCMs) comprising a polycaprolactone core surrounded by a silica shell were synthesized and their size, morphology, stability, and drug release kinetics were evaluated. The relationships between the composition of the SSCM-loaded poly(2-hydroxyethyl methacrylate) (*p*HEMA)-based hydrogels and their transparency, surface wettability, and equilibrium water content were determined. Scanning electron microscopy (SEM) images of SSCM–hydrogel systems showed the presence of intact SSCMs within the hydrogel matrix. Dexamethasone acetate (DMSA), a hydrophobic ophthalmic drug, was loaded into the SSCMs prior to their incorporation into the hydrogels. *In vitro* release of DMSA from the SSCM–hydrogels, with varying drug loading levels, was observed for up to 30 days. Overall, the incorporation of rod-like SSCMs within *p*HEMA-based hydrogels provided sustained release over prolonged periods while maintaining optical transparency. This delivery system may be suitable for use as a therapeutic soft contact lens material. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:627–637, 2013

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INTRODUCTION

Ocular diseases affect tens of millions of people across North America and the safe and effective treatment of these diseases has now become a growing multibillion-dollar industry (http://www.aao.org/newsroom/upload/Eye-Health-Statistics-April-2011.pdf). Ophthalmic drug delivery systems (DDSs) in the form of eye drops and ocular inserts are applied to the corneal surface to treat ailments of both the anterior and posterior segments of the eye.[1] If ocular diseases are left untreated, life-altering visual impairment and blindness may develop.[2–4] Approximately 90% of ocular DDSs are in the form of eye drops, which are applied in volumes ranging from 50 to 100 μL to the precorneal area, with greater than 75% of that volume being lost within the first 2–6 min.[5–8] Volume loss occurs by eye blinking, nasolacrimal drainage, and systemic absorption by the conjunctiva. After administration, only 1%–5% of the drug reaches the desired site of action, making eye-drop-based DDSs highly inefficient.[7]

Poor ocular bioavailability and the short duration of action limit the application of eye drops to diseases found in the anterior segments of the eye. Li and Chauhan[9] and del Amo and Urtti[10] have modeled drug delivery via contact lenses into the prelens and postlens tear film and subsequent uptake by the cornea. The simulation results showed that contact-lens-based DDSs are more effective than eye drops. Clinical studies have shown that soft contact lenses can result in significantly higher drug penetration than subconjuctival injections, thereby increasing ocular drug bioavailability and minimizing side effects.[11] Conventional treatments of posterior ailments such as posterior uveitis, diabetic macular edema, and age-related macular degeneration include invasive and repetitive intravitreal injections

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and/or surgical implants. Schultz et al.[12] recently demonstrated that sustained drug release from drug-loaded contact lenses enables significant drug levels to be achieved within tissues in the posterior segment of the eye. Because of their ability to enhance drug bioavailability and provide longer drug residence times, drug-eluting contact lenses may be used as an alternative to the methods commonly used to treat both anterior and posterior ailments of the eye.

Conventionally hydrophilic drugs such as ketorolac tromethamine and dexamethasone sodium phosphate are loaded into commercially available poly(2-hydroxyethyl methacrylate) (*p*HEMA) contact lenses by soaking the lenses in a buffer solution containing the drug.[13–15] Although soaked contact lenses are more efficient at delivering medications than eye drops, they typically only deliver their payload for a period of several hours.[14] For loading hydrophobic drugs, such as dexamethasone and dexamethasone acetate (DMSA), the two most commonly used methods are soaking the lenses in a drug–ethanol solution and directly entrapping the drug during polymerization of HEMA.[7,8,16–18] To date, several different approaches have been adopted to significantly increase the duration of drug release from contact lenses. These approaches include the incorporation of functional monomers[19,20] or other molecules that physically interact with the drug molecules,[21–25] the creation of drug reservoirs within the contact lens matrix via molecular imprinting,[26–30] and entrapment of a drug in nanosized or micron-sized systems dispersed within the lenses.[2,5,7,17,18,31–34]

Dexamethasone acetate is an anti-inflammatory drug commonly used in the treatment of acute and chronic posterior segment eye diseases.[35] However, the duration of DMSA release from *p*HEMA hydrogels lenses is limited to 3 days.[8] Thus, they cannot be used for long-term drug delivery applications. Block copolymer micelles formed from amphiphilic biocompatible block copolymers have been widely used as drug delivery vehicles.[36] The micelle core formed by the hydrophobic copolymer blocks can serve as a nanocontainer for hydrophobic drugs. In our previous work, core cross-linked polyethylene glycol-*block*-polycaprolactone (PEG-*b*-PCL) micelles containing the fluorescent probe 7-hydroxy-9H-(1,3-dichloro-9,9'-dimethylacridin-2-one (DDAO) were entrapped into a *p*HEMA hydrogel to extend the probe's release profile.[37]

In the current study, *p*HEMA-based hydrogels loaded with silica shell cross-linked micelles (SSCMs) of rod-like morphology were prepared and assessed for sustained delivery of the ophthalmic drug, DMSA. The use of this unique drug-loaded SSCM–hydrogel system as a drug-eluting soft contact lens may be a promising approach for treating anterior and posterior eye diseases through the extended delivery of hydrophobic ocular drugs.

MATERIALS AND METHODS

Materials

Methoxy poly(ethylene glycol)-*block*-polycaprolactone (MePEG-*b*-PCL) with a molecular weight (MW) of 2000 Da-*b*-2000 Da ($MePEG_{2k}$-*b*-PCL_{2k}) was synthesized and characterized using a previously published method.[38] ^1H NMR results were obtained using a Varian Mercury 400 spectrometer (400 MHz for ^1H) (Varian Inc., Palo Alto, CA) with deuterated water (D_2O) as the solvent and internal standard. DMSA, HEMA, methacrylic acid (MA), ethylene glycol dimethacrylate (EGDMA), tetraethoxysilane (TEOS), diethoxydimethylsilane (DEDMS), and lysozyme were purchased from Sigma–Aldrich Chemical Company (Oakville, ON, Canada). Prior to polymerization, HEMA and EGDMA were purified using inhibitor removal columns (Sigma–Aldrich Chemical Company, Oakville, ON, Canada). The photoinitiator Irgacure 2959 was kindly provided by Ciba Canada Ltd. (Mississauga, ON, Canada). All other reagents were of analytical grade and used as received.

Preparation of DMSA-Loaded SSCMs

$MePEG_{2k}$-*b*-PCL_{2k} micelles containing DMSA were prepared using the thin-film hydration method.[38,39] Briefly, a stock solution containing $MePEG_{2k}$-*b*-PCL_{2k} (50 mg) and DMSA (2 mg) was prepared in tetrahydrofuran. The solution was stirred overnight, dried under nitrogen to produce a thin film, and then kept under vacuum for 8 h. The dry copolymer–drug film was hydrated with double-distilled water (1 mL) at 65°C (i.e., above the melting point of the copolymer). The copolymer–drug solution was then vortexed, sonicated for 45 min, and then left to stir for another 3 days at room temperature. After 3 days, 16.9 μL of HCl (0.6 N) was added to the above solution to adjust the pH value to 2, and 85.7 μL of TEOS was added, followed by stirring at room temperature for 2 h. Finally, 13.1 μL of DEDMS was added to the mixture. In a separate study, high performance liquid chromatography (HPLC) analysis was used to confirm that incubation of DMSA under low pH conditions (i.e., pH = 2) for 2 h did not result in degradation of the drug (data not shown). After another hour, HCl and ethanol that formed from the hydrolysis of TEOS and DEDMS were removed by dialysis [MW cutoff (MWCO) 8000–10,000 Da] against distilled water until the pH was close to 6. The insoluble drug and silica species that formed during the monosilicic acid condensation reaction were removed from the SSCMs by centrifugation (Eppendorf 5804R, Mississauga, ON, Canada) at 4500 g for 10 min. The volume