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Surfactant-laden soft contact lenses for extended delivery of ophthalmic drugs

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ABSTRACT

Eye drops are inefficient means of delivering ophthalmic drugs because of limited bioavailability and these can cause significant side effects due to systemic uptake of the drug. The bioavailability for ophthalmic drugs can be increased significantly by using contact lenses. This study focuses on the development of surfactant-laden poly-hydroxy ethyl methacrylate (p-HEMA) contact lenses that can release Cyclosporine A (CyA) at a controlled rate for extended periods of time. We focus on various Brij surfactants to investigate the effects of chain length and the presence of an unsaturated group on the drug release dynamics and partitioning inside the surfactant domains inside the gel. The gels were imaged by cryogenic scanning electron microscopy (cryo-SEM) to obtain direct evidence of the presence of surfactant aggregates in the gel, and to investigate the detailed microstructure for different surfactants. The images show a distribution of nano pores inside the surfactant-laden hydrogels which we speculate are regions of surfactant aggregates, possibly vesicles that have a high affinity for the hydrophobic drug molecule. The gels are further characterized by studying their mechanical and physical properties such as transparency, surface contact angle and equilibrium water content to determine their suitability as extended wear contact lenses. Results show that Brij surfactant-laden p-HEMA gels provide extended release of CyA, and possess suitable mechanical and optical properties for contact lens applications. The gels are not as effective for extended release of two other hydrophobic ophthalmic drugs, dexamethasone (DMS) and dexamethasone 21 acetate (DMSA) because of insufficient partitioning inside the surfactant aggregates.

1. Introduction

Ocular disorders are mainly treated by using drug formulations in the form of eye drops [1] even though these are very inefficient in delivering therapeutic dosages to the patient's eye. Nearly 95–99% of the drug delivered via eye drops enters the systemic circulation by either conjunctival uptake or drainage into the nasal cavity, and that may cause severe side effects [2]. To overcome the drawbacks of eye drops, researchers have investigated several approaches for sustained ophthalmic drug delivery such as viscosity enhancers, corneal permeability enhancers, inserts, micro- and nanoparticles, and contact lenses. Contact lenses are particularly attractive for ophthalmic drug delivery as these significantly increase the residence time of the drug in the eye because of the geometric barrier provided by the contact lenses to the drug when it diffuses out from the gel matrix into the tear film. The residence time of the drug is more than 30 min in the presence of contact lenses [3,4] compared to around 15 min when eye drops are applied [5–9]. This significant increase in residence time increases the bioavailability of the drug by more than 50% and reduces wastage and side effects [10].

Drugs can be loaded in the contact lenses by either soaking the gels in drug solution [11–19], by dissolving drug in the monomer solution before polymerization [20–22] or by loading the drug in nanoparticles and dispersing them uniformly inside the gel matrix [23]. These drugs include cromolyn sodium, ketotifen fumarate, ketorolac tromethamine, dexamethasone sodium phosphate [24], timolol [25], pilocarpine [26] and fluoroquinolones [27]. While contact lenses will increase bioavailability, commercial lenses release ophthalmic drugs rapidly in a time of a few hours, and so are not suitable for extended drug delivery. The duration of release can be increased by increasing the binding of the drug to the gel matrix through molecular imprinting [28,29]. The duration of release can also be increased by incorporation of nano- or microparticles with large affinity for the drug inside the lenses. While nanoparticle-loaded lenses provide extended drug delivery, these require a two step process for fabrication: preparation of the particles, followed by entrapment in the lens matrix. It has also been proposed that the nanoparticles and/or nanodomains can be created in situ in one step by addition of surfactants to the polymerizing mixture. The surfactants can interact with the polymer matrix and form micellar aggregates creating hydrophobic sites

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inside the gel system where a hydrophobic substance will preferentially partition. Various groups have explored the idea of inhibiting drug transport due to the presence of surfactant micelles [30–39]. It is noted that in addition to attenuating drug release, the presence of surfactants in contact lenses could lead to other beneficial effects, such as an increase in corneal permeability [40–42] leading to increased bioavailability, and also increased wetting leading to better lubricity and comfort.

While a significant amount of work has been done in using surfactant micelles in gels for extended drug delivery, the majority of prior work focused on systems with polymer content less than 10%. Hydrogel contact lenses typically have about 60% polymer in the swollen state which competes with the surfactant aggregates for drug binding. It is thus essential that in order for the surfactants to retard drug transport in contact lenses, the surfactant aggregates must have a very high affinity for the drug compared to the hydrogel. Accordingly, to develop a contact lens suitable for extended delivery of a given drug, it is important to investigate the microstructure of the gel with particular focus on the micellar aggregates, and also investigate the mechanisms that impact the partitioning of the drugs in the aggregates. It is also equally important to investigate the effect of surfactant loading on the gel's physical properties relevant to contact lenses such as transparency, modulus, protein binding, wettability, and water content.

This paper is the first such exhaustive study that focuses on each of the issues listed above. The results of this study will be helpful in delivering CyA to eyes through contact lenses, and also in designing suitable contact lenses for delivering other ophthalmic drugs. Additionally, we explore fundamental issues related to drug and surfactant transport in the gels.

2. Materials and methods

2.1. Materials

Hydroxy ethyl methacrylate (HEMA) monomer, ethylene glycol dimethacrylate (EGDMA), Dulbecco's phosphate buffered saline (PBS), dexamethasone (DMS), dexamethasone acetate (DMSA), acetonitrile, lysozyme from chicken egg white, HPLC grade water, Brij 97, Brij 98, Brij 78 and Brij 700 were purchased from Sigma–Aldrich Chemicals (St Louis, MO). 2,4,6-Trimethylbenzoyl-diphenyl-phophineoxide (Darocur TPO) was kindly provided by Ciba (Tarrytown, NY). Cyclosporine A (CyA) was purchased from LC Laboratories (Woburg, MA). All the chemicals were reagent grade. Acetonitrile was filtered before use and all the other chemicals were used without further purification.

2.2. Preparation of surfactant laden gels

Surfactant-laden gels were prepared by polymerizing the monomer solution containing surfactant and drug mixed in a specific ratio. Briefly, 0.25, 0.6, 1.5 g of surfactant was dissolved in 10 ml of DI water to make three different surfactant solutions (corresponding to 2%, 4%, 8%, surfactant in dry gel respectively). Separately, 3.5 mg of drug was dissolved in 2.7 ml of HEMA monomer and stirred at 600 rpm for a period of 5 h. Next 15 μl of the crosslinker and 2 ml of surfactant solution were added to the 2.7 ml of drug loaded monomer. The solution was degassed by bubbling nitrogen gas through it for 10 min followed by addition of 6 mg of UV initiator (TPO) and stirring the solution for 10 min. The solution was then poured between two glass plates separated by a spacer and the gel was cured by irradiating UVB light (305 nm) for 40 min from an ultraviolet transilluminator UVB-10 (Ultra·Lum, Inc.). Four different spacers, 100, 200, 400 and 800 μm in thickness were utilized to synthesize gels of various thicknesses. Control, drug loaded p-HEMA gels without surfactants were prepared by following procedures identical to those described above except that the 2 ml of surfactant solution was replaced by 2 ml of DI water.

2.3. Drug release

After polymerization, each gel was removed from the glass mold and was cut into smaller pieces that weighed about 40 mg in the dry state. These 40 mg gels were used in all experiments described below. As the thickness of the gel was varied, the size of the gel piece was adjusted to a maintain similar weight for all the gels used in the study. Two sets of experiments were performed for the drug release studies. In the first set of experiments, gel was soaked in 3.5 ml of PBS and measurements were taken until equilibrium was reached for the drug. In the second set, gel was soaked in 3.5 ml of PBS and PBS was replaced every 24 h, mimicking perfect sink conditions for the release experiments. Equilibrium experiments were conducted for all three drugs explored in this study (CyA, DMS, and DMSA), whereas PBS replacement experiments were performed for CyA only.

2.4. Drug detection

CyA concentration was measured using HPLC (Waters, Alliance System) equipped with a C_{18} reverse phase column and UV detector [43]. The mobile phase composition was 70% acetonitrile and 30% DI water, and the column was maintained at 60 °C. The flow rate was fixed at 1.2 ml min^{-1} and the detection wavelength was set at 210 nm. The retention time for CyA under these conditions was 4.5 min, and the calibration curve for the area under the peak vs. concentration was linear ($R^2 = 0.995$). DMS and DMSA were detected using a UV– vis spectrometer (Thermospectronic Genesys 10 UV) by measuring the absorbance spectra over a range of 190–290 nm. The absorbance data for the release experiments of DMS and DMSA were converted to the respective concentration value by a de-convolution technique as reported earlier [44].

2.5. Surfactant release

The rates of surfactant release were measured in 3.5 ml of DI water with water replacement after each measurement to maintain perfect sink conditions. The surfactant concentration in the release medium was determined by measuring the surface tension (σ), which was then related to the concentration through a $\sigma(C)$ calibration curve. The surface tension was measured by using a Wilhelmy plate (sand blasted platinum plate) attached to a Scaime France microbalance which was further connected to a Stathan Universal transducer (SC001). A detailed description of the process for measuring surfactant concentration by surface tension measurements has been reported earlier [39].

2.6. Lysozyme sorption

A lysozyme solution was prepared by adding 40 mg of lysozyme to 40 ml of PBS. The 8% surfactant-laden gels (about 40 mg in weight) were soaked in 3.5 ml of lysozyme solution and the amount of lysozyme that was taken up by the hydrogels was monitored by UV detection in the wavelength range 240–340 nm. The concentration of lysozyme was evaluated following a similar protocol as reported above for DMS and DMSA.

2.7. Preparation and cryo-SEM of hydrogels

All samples were soaked in 1× PBS buffer for at least 24 h. The hydrogel samples were trimmed down to approximately 1 cm × 1 cm in size and mounted vertically on the cryo-SEM sample holder with a small amount of Tissue-Tek adhesive (Sakura). The samples were rapidly plunged into liquid nitrogen at a temperature below −190 °C (Gatan, Alto 2500), withdrawn into a vacuum transfer device under the protection of a high vacuum, and transferred into the cryo-preparation chamber where the temperature was maintained at −130 °C and the anticontaminator at around −188 °C. The hydrogel samples were freeze fractured using the flat edge of a cold knife maintained at −130 °C and sublimated for 5 min at −95 °C to etch away surface water and expose the internal structural features. After sublimation, the temperature of the stage was adjusted back to −130 °C and the samples were sputter coated with platinum at 11 mA for 100 s. The samples were then transferred into the main chamber of the field emission SEM (Hitachi S-4800) via an interlocked airlock and mounted onto a cold stage module (−130 °C) fitted to the SEM stage. Images were acquired at a voltage of 2 kV.

2.8. Dynamic mechanical analysis

A dynamic mechanical analyzer (DMA Q800, TA instruments) was used to determine the mechanical properties of different surfactant-laden systems synthesized above. For this study 400 μm and 800 μm thick gels were utilized to avoid breaking of the gel during the experiment. A hydrated gel was mounted on the clamp and the gel was kept submerged in DI water at room temperature during the experiment. Gel response in the form of storage and loss modulus of the gel was determined by applying tensile force in the longitudinal direction while keeping the gel tightly screwed between the clamps by applying a preload force of 0.01 N. To determine the linear viscoelastic range, strain tests were first conducted at a frequency of 1 Hz followed by frequency sweep (1–35 Hz) measurements performed for all the samples at 20 μm strain.

2.9. Surface contact angle

Surface contact angles were measured for all the surfactant-laden systems with 8% loading to investigate the effect of surfactant release on wettability. The contact angles were measured by captive bubble technique with a Drop Shape Analyzer (DSA100, KRÜSS). This technique was preferred over the sessile drop technique to eliminate contact angle change due to sample drying during measurements. A 200 μm thick gel was mounted on a glass slide which was then placed on a water filled cuvette with the lens submerged in water. An air bubble was created by an