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Drug and surfactant transport in Cyclosporine A and Brij 98 laden p-HEMA hydrogels

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Abstract

Surfactants are commonly incorporated into hydrogels to increase solute loading and attenuate the release rates. In this paper we focus on understanding and modeling the mechanisms of both surfactant and drug transport in hydrogels. Specifically, we focus on Brij 98 as the surfactant, Cyclosporine A (CyA) as the hydrophobic drug, and poly-hydroxy ethyl methacrylate (p-HEMA) as the polymer. The models developed here are validated by experiments conducted with gels of different thicknesses and surfactant loadings. Also the model is compared with prior experimental studies in literature. The model predicts that the percentage surfactant as well as drug release scales as $1/(\text{surfactant loading})^{0.5}$, and thus a four fold increase in surfactant loading leads to a two fold reduction in percentage release for both drug and surfactant at a given time. The models for the surfactant and drug release are fitted to the experimental data to obtain values of 1.44×10^{-14} m^2/s for CyA diffusivity and 414.4 for the partition coefficient between drug concentration inside the micelle and that in the gel. These models can be very helpful in tuning the drug release rates from hydrogels by controlling the surfactant concentration. The results also show that Brij 98 loaded p-HEMA exhibit an extended release of CyA and so contact lenses made with this material can be used for extended ocular delivery of CyA, which is an immunosuppressant drug commonly used for treatment of various ocular ailments.

Keywords: Cyclosporine A; p-HEMA; Transport; Model; Micelles; Aggregation; Brij 98

1. Introduction

Controlling the rate of release of solutes from hydrogels is important for a number of applications, particularly in the pharmaceutical area. The rate of release strongly depends on the interaction of the solutes such as drugs with the hydrogel, and this interaction can be altered by incorporation of surfactants into the gel matrix. This approach is useful for increasing the loading of hydrophobic drugs into the hydrogels and also for controlling the drug release rates. Both of the above effects are caused by formation of surfactant aggregates inside the hydrogel. Hydrophobic drugs can partition into these aggregates leading to enhanced loading, and the drug-laden micelles can act as depots of drug leading to extended drug release. In some cases such as cationic systems, the drug and the surfactant molecules together form the micelles.

Paulsson and Edsman explored diffusion of hydrophobic drugs in carbopol gels loaded with Brij 58 and sodium dodecyl sulfate (SDS) and showed that as the hydrophobic nature of the drugs was increased, there was a significant decrease in the diffusion rates [1]. They concluded that the reduction in diffusion rate could be attributed to the lipophilic interactions between the drug and the surfactant micelles. They also showed that the interactions between charged drug and oppositely charged surfactant could further decrease the diffusion of the drug [2]. In another study, they showed that the interaction of polymer with the drug can also control the release rates [3]. The polymer content in all their formulations was less than 2%. Lin et al. also explored carbopol gels and showed that pluronic F-127 surfactant can be used to control the release of the drug especially if the gel and surfactant are mixed in a suitable ratio [4]. Liu et al. used an anionic surfactant sodium dodecyl sulfate (SDS) to achieve control release of a hydrophobic drug camptothecin (CPT) from agarose hydrogels by first solubilizing the drug in surfactant mixture and then loading it in the hydrogel [5]. They

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later on explored use of cationic surfactant dodecyl trimethyl ammonium bromide (DTAB) to perform a similar study [6]. In both these works, researchers showed that the release of CPT was slowed down with increasing concentration of surfactant. Concheiro et al. explored the changes in microviscosity of mixtures due to presence of surfactants and suggested that these systems could be used in ophthalmic applications to increase the retention time of eye drops and thus prolong the release of the drug to the ocular tissues [7]. The gel–surfactant–drug interactions and the consequences on the drug release rates have been reviewed in detail by Concheiro and Alvarez-Lorenzo [8]. While the literature contains a number of experimental studies in the general area of transport in surfactant-laden hydrogels, to our knowledge, no model has been developed for these systems. The goals of this paper are to understand and model the transport of both surfactant and drug from the hydrogels. We specifically focus on p-HEMA hydrogels that are loaded with Brij 98 surfactant and drug CyA. We are specifically interested in this system because of our interest in extended delivery of ophthalmic drugs such as CyA from p-HEMA contact lenses to increase the bioavailability of the drug on the ocular surface. CyA is an immunosuppressant drug commonly used for treatment of a number of ocular ailments including dry eyes [9], uveitis in children and adolescents [10], vernal keratoconjunctivitis [11] and peripheral ulcerative keratitis [12].

It is noted that a majority of the studies listed above have focused on gels with small polymer volume fraction of less than 10% and thus large pore sizes. The polymer fraction in the p-HEMA gels explored here is about 60%, with pore sizes of about 2 nm. While this paper focuses on a specific set of drug, surfactant and polymer, the model developed here is expected to be valid for a wide variety of systems.

2. Materials and methods

2.1. Materials

2-Hydroxyethyl methacrylate (HEMA) monomer, ethylene glycol dimethacrylate (EGDMA), Dulbecco's phosphate buffered saline (PBS), acetonitrile, HPLC grade water, and polyoxyethylene (20) oleyl ether (Brij 98) were purchased from Sigma–Aldrich Chemicals (St. Louis, MO). 2,4,6-Trimethylbenzoyl-diphenyl-phosphineoxide (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 after receiving and all the other chemicals were used without further purification.

2.2. Preparation of surfactant laden gels

Surfactant solutions of three different concentrations were prepared by adding 0.25, 0.6, 1.5 g of the surfactant to 10 ml de-ionized (DI) water and then stirring the mixture at 600 rpm and at room temperature for a period of about 10 h. Separately, 3.8 mg of CyA was dissolved in 2.7 ml of HEMA monomer and stirred at 600 rpm for a period of 5 h. 15 μl of the crosslinker (EGDMA) and 2 ml of surfactant solution were added to the 2.7 ml of drug–HEMA mixture. The solution was then degassed by bubbling nitrogen for 10 min. Next, 6 mg of the initiator (TPO) was added and the solution was stirred at 300 rpm for 10 min to completely solubilize the initiator. The solution was then poured in between two glass plates that were separated either by a 200 μm (thick gels) or 100 μm (thin gels) thick spacer. The mold was then placed on Ultraviolet transilluminiator UVB-10 (UltraLum, Inc.) and the gel was cured by irradiating UVB light (305 nm) for 40 min. To synthesize p-HEMA gels without surfactants, 2 ml of the surfactant solution was replaced by 2 ml DI water. These gels are referred to as pure gels in the following sections.

2.3. Drug release experiments

After polymerization, each gel was removed from the glass mold and cut into smaller pieces that were about 1.5 cm × 1.5 cm × 200 μm for the thick gels and 1.5 cm × 3 cm × 100 μm for the thin gels, with each gel weighed nearly 40 mg. 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 the drug concentrations in the release medium was measured periodically until the drug flux approached zero. In the second set of experiments, we attempted to create perfect sink conditions in the release medium of 3.5 ml PBS by replacing the medium every 24 h. CyA concentration was measured using an HPLC (Waters, Alliance System) equipped with a C_{18} reverse phase column and a UV detector. 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 and the detection wavelength was set at 210 nm. The retention time for CyA under these conditions was 5.3 min, and the calibration curve for area under the peak vs concentration was linear ($R^2 = 0.98$).

2.4. Surfactant release experiments

The rates of surfactant release from the gels was measured by soaking them in 3.5 ml DI water and replacing the release medium at regular intervals. The surfactant concentration in the release medium was determined by measuring 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). The transducer was calibrated by using DI water ($\sigma = 72$ mN/m) and acetone ($\sigma = 23$ mN/m) as standards. The Wilhelmy plate was rinsed with DI water and acetone followed by annealing till red hot using a propane burner. The annealing process was done to remove impurities which rinsing was not able take away from the platinum surface. This process was repeated before every measurement and the plate was left to cool for one minute before taking the measurement. The solution was allowed to equilibrate for an hour prior to the measurement to ensure that the