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Aggregation and transport of Brij surfactants in hydroxyethyl methacrylate hydrogels

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ABSTRACT

Surfactant loaded polymeric hydrogels find applications in several technological areas including drug delivery. Drug transport can be attenuated in surfactant loaded gels through partitioning of the drug in the surfactant aggregates. The drug transport depends on the type of the aggregates and also on the surfactant transport because diffusion of the surfactant leads to dissolution of the aggregates. The drug and the surfactant transport can be characterized by the surfactant monomer diffusivity D_s, and the critical aggregation concentration C^*. Here we focus on the transport in hydroxyethyl methacrylate (HEMA) hydrogels loaded with three different types of Brij surfactants. We measure transport of a hydrophobic drug cyclosporine and the surfactant for surfactant loadings ranging from 0.1% to 8%, and utilize the data to predict the values of D_s, and C^*. We show that the predictions based on surfactant transport are significantly different from those based on modeling the drug transport. The differences are attributed to the assumption of just one type of aggregate in the gel irrespective of the total concentration. The transport data suggests existence of multiple types of aggregates and this hypothesis is validated for Brij 98 by imaging of the microstructure with free fracture SEM.

1. Introduction

Surfactants are frequently loaded in hydrogels to tailor the physical and transport properties. Surfactant incorporation in hydrogels can alter solute binding and transport properties [1–6], structure and swelling behavior [7–12], and provide additional benefits such as antibacterial protection [13,14]. The surfactant loading in several applications is above the critical aggregation limit and so the excess surfactant forms aggregates of various types including micelles and vesicles. The presence of the surfactant aggregates significantly impacts a number of properties including transport of the surfactant and solutes that can selectively partition in the aggregates. There is extensive literature on using surfactant aggregates in gels to facilitate extended release of various solutes including proteins and drugs [1]. In most applications of surfactant-loaded gels, the loaded surfactant is not crosslinked to the matrix, and so it could also diffuse out of the gels. Surfactant diffusion could potentially be toxic and furthermore the diffusion of the surfactant will have a significant impact on the transport of other solutes. Thus it is important to understand and model the transport of surfactant in the gels, particularly above the critical aggregation concentration.

A model for surfactant release from hydrogels laden with surfactant aggregates has been proposed and validated [15]. The model predicts that the surfactant release from the gel is governed by the following equation:

$$\%\text{Surfactant Release} = \sqrt{2D_S C^*}\sqrt{\frac{t}{C_P h^2}} \times 100 \quad (1)$$

where % Surfactant Release is the ratio of the cumulative release and the total surfactant loading, D_s is the surfactant diffusivity, C^* is the critical aggregation concentration (CAC), t is time, C_p is the concentration of the surfactant present as aggregates inside the hydrogel, and h is the half-thickness of the hydrogel. The above equation is valid for diffusion of any solute that is loaded in the gel significantly above the saturation limit and so a large fraction of the solute precipitates into aggregates. This equation is the equivalent of the Higuchi equation that is commonly utilized to model drug release from ointments when drug is present as a suspension [16]. The model is based on assuming that the surfactant flux occurs only due to the diffusion of the surfactant monomer. The aggregates cannot diffuse but as soon as the concentration of the free surfactant in the gel is reduced below the critical aggregation concentration, the aggregates rapidly break releasing the sur-

Abbreviations: C*, CAC, critical aggregation concentration; HEMA, hydroxyethyl methacrylate; CyA, cyclosporine A.

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factant into the gel. Thus, as time progresses a zone is created near the surface which is devoid of any aggregates. The prediction of Eq. (1) is valid only as long as the thickness of the aggregate free zone is less than the half-gel thickness, i.e., the aggregates have not entirely dissolved. Also Eq. (1) is only valid when the total surfactant loading is significantly above the solubility limit. Kapoor and Chauhan explored transport of Brij surfactants of various molecular weights and a hydrophobic drug cyclosporine in p-HEMA gels [17]. The transport data for both the surfactant and the solute was shown to be diffusion controlled and based on the above equation, a plot of surfactant release vs. $\sqrt{\frac{t}{C_p h^2}}$ should be a straight line, which was verified by experiments for four different Brij surfactants: Brij 78, Brij 97, Brij 98 and Brij 700. The values of $D_s C^*$ for the four Brij surfactants was obtained from the fitting of the experimental data to Eq. (1). Also published experimental data for other systems was shown to satisfy the relationship predicted by Eq. (1)[15].

While the experimental data obtained by Kapoor and Chauhan [15,17] satisfied the scaling predicted by the model, the validity of the model was not proven because the values of D_s and C^* were not obtained independently. In this paper we develop a generalized model for the surfactant transport that is valid at concentrations even slightly larger than the solubility limit. Also we aim to further explore the mechanisms of the surfactant transport by first measuring D_s and C^* independently. By combining transport data with SEM imaging, we show that while the model proposed by Kapoor and Chauhan [15,17] includes the key mechanisms, some of the assumptions regarding the microstructure are not correct, and that leads to errors in predicting transport. The results of this work will improve our fundamental understanding of surfactant transport in gels loaded at concentrations above the aggregation limit. The results could also be useful in designing various biomedical systems for control release of various solutes.

2. Materials and methods

2.1. Materials

2-Hydroxyethyl methacrylate (HEMA) monomer, ethylene glycol dimethacrylate (EGDMA), Dulbecco's phosphate buffered saline (PBS), acetonitrile, polyoxyethylene(20) stearyl ether (Brij 78), polyoxyethylene(10) oleyl ether (Brij 97), polyoxyethylene(20) oleyl ether (Brij 98) and HPLC grade water were purchased from Sigma–Aldrich Chemicals (St. Louis, MO). 2,4,6-trimethylbenzoyl-diphenyl-phophineoxide (TPO) was kindly provided by Ciba (Tarrytown, NY). 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 and drug laden gels

The surfactant laden gels were prepared by polymerizing the monomer solution containing surfactant and drug mixed in specific ratio. Briefly, specific amounts of surfactants were dissolved in DI water to make surfactant solutions of compositions such that the surfactant loadings in the dry gel ranged from 0.1% to 8%. 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 cross-linker and 2 mL of surfactant solution were added to 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 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 transilluminiator UVB-10 (Ultra Lum, Inc.). Control drug loaded p-HEMA gels without surfactants were prepared by following procedures identical to those described above except that the 2 mL surfactant solution was replaced by 2 mL DI water. Control gels without any drug were synthesized in a similar manner as described above except that the drug was not mixed in the monomer solution before polymerization. After polymerization, each gel was removed from the glass mold, and was cut into smaller square pieces that were dried at room temperature for two days before being used for any experiments.

2.3. Surfactant transport

Square gel pieces about 1.5 × 1.5 cm in size and 40 mg in weight were utilized for surfactant release experiments. The rates of surfactant release from the gels were measured under sink conditions by soaking 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 tensions (σ), which was then related to the concentration through a $\sigma(C)$ calibration curve. The surface tension was measured by using a sand blasted platinum Wilhelmy 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 (σ = 72 mN/m) and acetone (σ = 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. This process was repeated before every measurement and the plate was left to cool for 1 min before taking the measurement. The solution was allowed to equilibrate for an hour prior to the measurement to ensure that the surface coverage was in equilibrium with the bulk concentration. It was also ensured that the surface area to volume ratio was sufficiently small to cause a negligible change in bulk concentration due to adsorption of the surfactant on the surface.

2.4. Drug transport

Square gel pieces about 1.5 × 1.5 cm in size and 40 mg in weight were utilized for drug release experiments. Drug release kinetics was measured at room temperature by soaking the gel in 3.5 mL PBS, which was replaced every 24 h. These experiments were conducted till about 60% of the loaded drug had diffused from the gel matrix. The drug 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 4.55 min, and the calibration curve for area under the peak vs. concentration was linear (R^2 = 0.995).

2.5. Cryo-scanning electron microscopy (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 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 the 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 sput-