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Polymeric hydrogel thin film synthesis via diffusion through a porous membrane

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ABSTRACT

We report here a simple, versatile bi-cell-based platform for preparing crosslinked polymeric hydrogel thin films. Briefly, a nanoporous membrane is used to separate two solutions: one containing crosslinking molecules and the other containing oligomers. The crosslinking molecule diffuses through the membrane and reacts with the oligomer to form a polymeric film at the surface of the nanopore membrane. In this paper, a proof-of-concept experiment is described using crosslinkers with imidoester moieties (dimethyl 3,3′-dithiobispropionimidate (DTBP) or dimethyl suberimidate (DMS)) and chitosan oligomers. Crosslinking with DTBP or DMS also conferred degradability to the chitosan film. The film formation was confirmed and its morphology examined with electron microscopy. The chitosan film degradation was quantified by monitoring the transport of gold nanoparticles through the chitosan film after a degradation treatment. The film synthesis method presented here can potentially be used to prepare functional hydrogel thin films for biosensors, coatings and drug delivery systems in an inexpensive, high-throughput manner.

1. Introduction

Polymer hydrogels are widely studied in tissue engineering, drug delivery and controlled release of chemicals or particles, which applications require biocompatibility, responsiveness to external stimuli, or encapsulation of foreign substances such as chemicals, particles or cells [1–3]. When hydrogels are prepared as thin films, they can be used to functionalize a substrate surface and exhibit faster response times to external stimuli than their bulk counterparts. This makes hydrogel thin films one of the materials of choice for use in biosensors and actuators [4,5].

Hydrogel thin films and polymer brushes have been successfully synthesized by several methods, such as free-radical polymerization [6], plasma polymerization [7], high-energy irradiation [8], layer-by-layer assembly [9], self-assembly [10] and surface initiated polymerization [11]. However, the specialized equipment needed for many of these methods, and the time/labor intensive steps of these approaches, can be a drawback when access to the expensive equipment is limited or when a component of the hydrogel exhibits a time-sensitive property (for example, photobleaching or deterioration).

We demonstrate here for the first time a simple, one-batch bi-cell approach that can be used to create crosslinked polymer hydrogel thin films. This technique requires no specialized instrumentation or intensive experimental steps. It is based on a heterogeneous reaction that occurs at the surface of a nanoporous filter membrane substrate. As a proof of concept, we fabricate a hydrogel thin film using chitosan, a biopolymer that is gathering increased research interest for its biocompatibility and structural properties [12–14]. The method described here can easily confer stimuli-responsiveness to chitosan films, and we demonstrate this through a degradation response of the fabricated chitosan film upon exposure to glutathione or compounds containing free amine groups.

2. Experimental

Materials: The crosslinkers dimethyl 3,3′-dithiobispropionimidate (DTBP) and dimethyl suberimidate (DMS) were purchased from Thermo Scientific Pierce, chitosan oligosaccharide lactate (MW 5000, deacetylation degree $\geq$90%) and glutathione (GSH) from Sigma Aldrich, ethylenediamine (EDA) from Acros Organics, dithiothreitol (DTT) from Fisher BioReagents™, BBI™ unconjugated gold colloid (5 nm) from Ted Pella, and Isopore™ polycarbonate (PC) filter membranes (600 nm pore diameter) from EMD Millipore. Chemical structures are shown in Fig. 1. All water was obtained using a Milli-Q® Integral system.

Preparation of chitosan films: PC membranes were taped (electroplating tape, 3M Company) to the bottom of a custom-built

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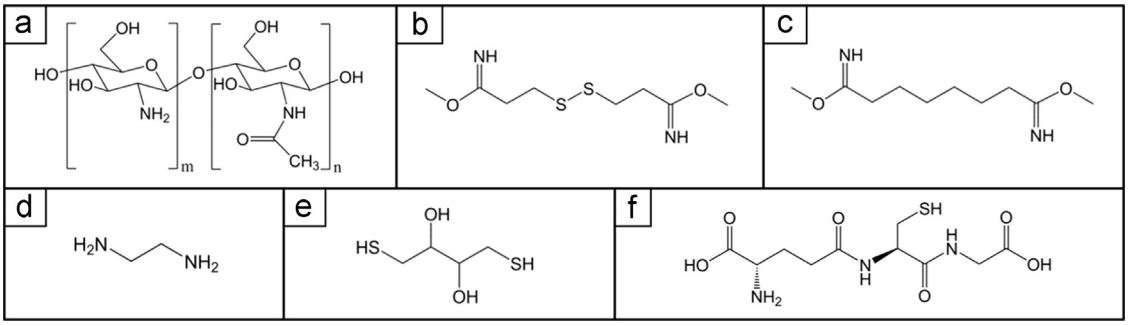

Fig. 1. Chemical structures of (a) chitosan, (b) DTBP, (c) DMS, (d) EDA, (e) DTT and (f) glutathione.

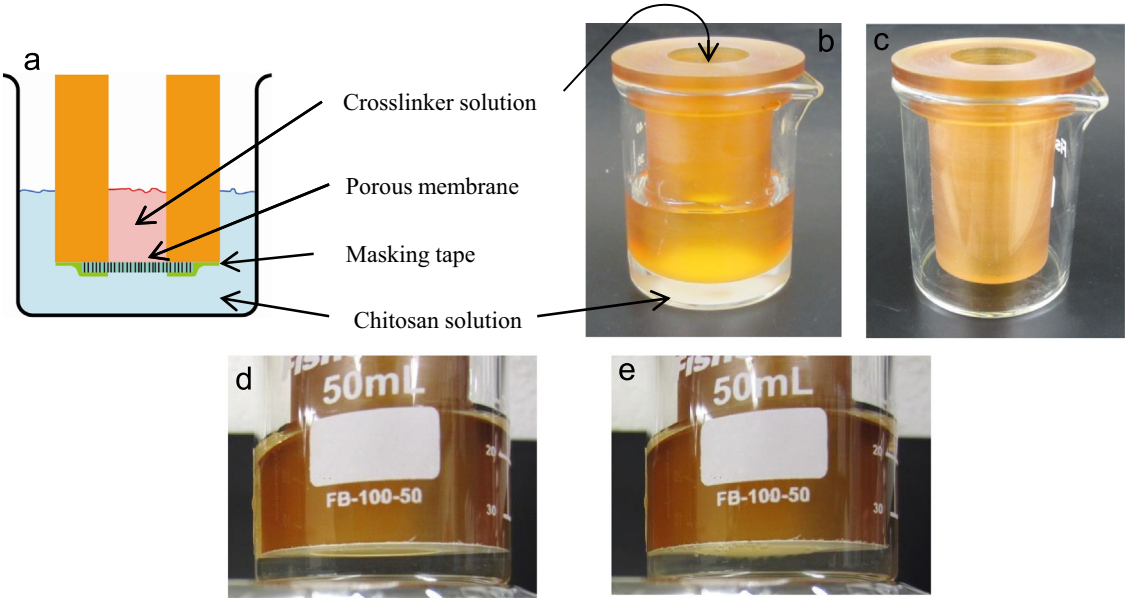

Fig. 2. Heterogeneous synthesis apparatus (a) schematic diagram and photos of the apparatus (b) with solutions, (c) without solutions, (d) at time = 0 s and (e) after 3 h of reaction.

annular apparatus (Fig. 2). The membrane pores were then wetted with water in a vacuum desiccator. The apparatus was then inserted into a beaker containing 0.5% (w/v) chitosan in water. A 100 mM carbonate buffer solution (pH 9.3) that was also 15 mM in either DTBP or DMS was added to the apparatus' inner cavity. The heights of the two solutions were equal. After 4 h the sample was removed from the apparatus, rinsed with water and dried in a desiccator overnight.

Treatment of chitosan films for degradation: Chitosan films, still attached to the PC membranes, were submersed in 100 mM phosphate buffered saline (PBS), pH 7.4, with also 10 mM of either GSH, EDA or DTT for 108 h at 37 °C, then rinsed with water. Control treatment with only PBS was also performed.

Characterization of chitosan films: Degradation of the chitosan films was characterized by measuring the transport of gold nanoparticles through the film by UV–vis spectrometry (Jenway 6505). The intensity of absorption can be directly correlated to the colloid concentration [15] using the peak absorption at 515 nm (Fig. S1). The sample was placed in a custom-built U-cell, separating the two half-cells; the colloid solution (5×10^{13} particles mL^{-1}) was added to one side of the U-cell, and water to the other (Fig. S2). The absorption was measured after 24 h of diffusion. Morphology of the chitosan films was examined with field-emission scanning electron microscopy (Zeiss Auriga FE-SEM).

3. Results and discussion

Chitosan film synthesis: Similar to the heterogeneous synthesis method previously reported by Martin et al. [16,17], we used a porous membrane to separate a chitosan polymer solution from a crosslinker solution. Fig. 2a shows a schematic of our reaction apparatus with the crosslinker solution above the membrane and the chitosan solution below. Photos of the apparatus are also shown with and without solutions in Fig. 2b and c, respectively. We found that a film forms on the lower surface of the membrane within 3 h (Fig. 2d and e) and that this gel continues to grow until eventually the entire chitosan solution is gelled. After 4 h of reaction the hydrogel is 1.6 ± 0.5 mm thick, and after complete drying it is 2.8 ± 0.7 μm thick.

A decrease in chitosan's solubility and the crosslinking reaction each contribute to the film formation. As the carbonate buffer (pH 9.3) in the crosslinker solution mixes with the chitosan solution (pH 4.2), it increases the pH of the chitosan solution and causes the chitosan to form a gel [8]. Indeed, a film forms with longer mixing time even without crosslinkers present; however, these films are insubstantial and degenerate during subsequent rinsing steps. When either DTBP or DMS is present, their imidoester moieties react with the free amines on the chitosan to form an imidoamide bond [18–20] (Fig. S3). This approach yields firmer films that do not lose integrity during subsequent handling.