

Polymer communication

Tuning biodegradable hydrogel properties via synthesis procedure



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ABSTRACT

Biodegradable hydrogels have become a rapidly expanding area of research for biomedical applications. Poly(β -amino ester) (PBAE) biodegradable hydrogels, in particular, have been studied extensively because of the ease of synthesis and range of properties exhibited. In this work, PBAE macromers were created with poly(ethylene glycol) diacrylate (PEGDA), diethylene glycol diacrylate (DEGDA), and isobutylamine. Many methods have been presented that allow control over the resulting hydrogel behavior. Here, properties were varied by combining multiple diacrylate components in the macromer synthesis step (single macromer (SM)) or through the combination of multiple macromers prior to polymerization (double macromer (DM)). The exhibited properties are a result of the hydrophilic/hydrophobic contributions of the different diacrylate molecules to the macromer. The SM systems exhibited linear degradation profiles, the rate of degradation increased as the PEGDA concentration increased. DM systems exhibited a multiphase degradation profile as a result of the combination of macromers with different hydrophilic properties.

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1. Introduction

Biodegradable hydrogels are commonly selected for biological applications due to their properties which can mimic those of natural soft tissue [1]. The added benefit of degradation *in vivo* allows the use of a single procedure to insert (e.g., inject or surgically implant) the hydrogel with no need for removal after its useful lifetime [2]. Researchers have studied a wide range of biodegradable hydrogels for applications in biology and medicine [2–5]. Poly(β -amino esters) (PBAE) biodegradable hydrogels are one specific class that has gained attention in recent years due to their readily available/inexpensive components, ease of synthesis, and no requirement of purification [4]. PBAE hydrogels can be synthesized through a step-growth conjugate addition reaction between a

diacrylate and amine component to form a diacrylate macromer for free radical polymerization [4]. The relatively simple processing of the PBAE systems makes them ideal for materials for studying the effects of different variables on the resulting hydrogel properties.

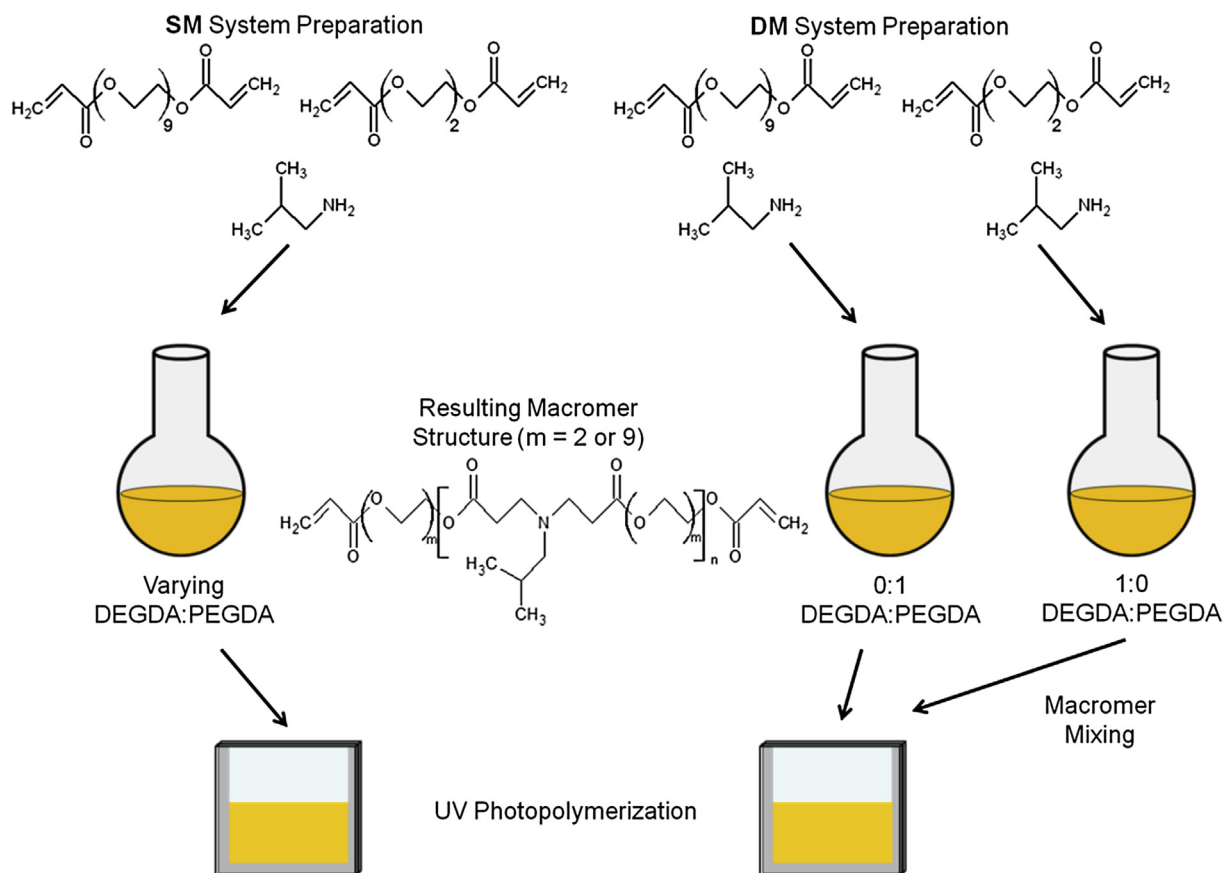
There are many methods for tuning the properties of biodegradable hydrogel systems. In the case of PBAE systems, polymer properties have been controlled through the choice of chemicals in the synthesis [4], the molar ratio of diacrylate to amine [6,7], the addition of crosslinking agents [8], and the time allowed for the macromer synthesis reaction to occur [9]. In this work, the results of using another tuning parameter are explored. Here, the overall system chemical makeup is kept constant, but the synthesis procedure is varied (Scheme 1). This approach could be advantageous in the situation where a certain chemical ratio is shown to provide favorable properties for a given application (i.e., cell responses or degradation rate). This enables the hydrogel physical properties to be altered without changing the basic chemical composition, as occurs with the other methods of tuning.

This research outlines a new method in which three chemicals are used in each system: two diacrylates, poly(ethylene glycol) diacrylate (PEGDA) and diethylene glycol diacrylate (DEGDA), and an amine, isobutylamine. For one synthesis procedure, a single macromer was synthesized using the two diacrylate components with the amine in a single batch reaction; thus, these systems are

Abbreviations: DEGDA, diethylene glycol diacrylate; DM, double macromer; DMPA, 2,2-dimethoxy-2-phenylacetophenone; FTIR, Fourier transform infrared spectroscopy; GPC, gel permeation chromatography; PBAE, poly(β -amino ester); PBS, phosphate buffered saline solution; PEGDA, poly(ethylene glycol) diacrylate; SM, single macromer; THF, tetrahydrofuran.

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Scheme 1. Methods of preparation – preparation methods showing the two protocols for systems of the same overall chemical composition.

referred to as single macromer (SM). In the other synthesis procedure, two unique macromers were synthesized using each diacrylate individually with the amine, and hydrogels were then formed from a combination of the macromers; these are called double macromer (DM). Significant differences in the properties of the hydrogel system, most importantly in the degradation profiles, were shown in hydrogel systems with the same chemical composition but differences in the order of macromer synthesis and mixing. The SM systems exhibited linear degradation profiles, whereas the DM systems showed two distinct phases of mass loss. Both systems exhibited behavior that could be practical in a range of applications, including drug delivery and tissue engineering.

2. Experimental

2.1. Materials

Diethylene glycol diacrylate (DEGDA) and poly(ethylene glycol) diacrylate ($N = 400$) (PEGDA) were purchased from Polysciences, Inc. (Warrington, PA). Isobutylamine and 2,2-dimethoxy-2-phenylacetophenone were purchased from Sigma Aldrich (St. Louis, MO). All materials were used as received.

2.2. Methods

2.2.1. Macromer synthesis & hydrogel polymerization

Macromers were prepared according to previous research [4,9,10] with slight alterations. In this study, two different types of hydrogels systems were created from five different macromer synthesis systems (Scheme 1). In the macromer synthesis

procedure, the diacrylate (or combination of two diacrylate components) and amine were combined in a sealed 100 mL round bottom flask and reacted at 85 °C for 48 h. The hydrogels created from these macromer combinations are referred to as single macromer (SM) systems because they are composed of one macromer synthesized through the reaction of the two diacrylates and the amine component. For these single macromer systems, a nomenclature was developed to describe the chemicals used and the ratios of each (Scheme 2). For instance, in AH6 1.2(1:1) the prefix AH6 indicates the chemicals used (prefixes were taken from Anderson et al. [4]), the number before the parenthesis indicates the molar ratio of total diacrylate to amine (here 1.2:1), and the ratio in the parenthesis indicates the molar ratio of DEGDA (i.e., A) to PEGDA (i.e., H), representative of the hydrophobic to hydrophilic ratio. In the second set of hydrogels, the two single macromers (AH6 1.2(1:0) and AH6 1.2(0:1)) were combined after the macromer synthesis but prior to polymerization (Scheme 2). This set of systems will be referred to as double macromer (DM) because they were formed with two macromer components mixed prior to polymerization. In all five macromer systems synthesized and all resulting hydrogels, the total diacrylate to amine molar ratio is 1.2:1. Systems will be referred to by their preparation method (SM or DM) and the overall hydrophobic to hydrophilic ratio represented by the DEGDA:PEGDA molar ratio for the remainder of this paper.

Hydrogels were polymerized using UV photopolymerization of the previously synthesized macromer with no further purification. Briefly, the macromer was weighed and combined with a mixture of DMPA (1 weight percent) in ethanol solvent (50 weight percent). All percentages are based on the initial macromer mass weighed.

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