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Synthesis and characterization of biodegradable poly(ether-ester) urethane acrylates for controlled drug release

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ABSTRACT

Three polyether-ester triblock diols, with various molecular weights, were synthesized from ε-caprolactone and polyethylene glycol and used, with diisocyanates, as soft segments for the preparation of polyurethane acrylate oligomers. The polyurethane acrylates were used to generate cross-linked polyurethane films via UV initiated polymerization with and without cargo incorporation. Degradation experiment indicated that in PBS/H_2O_2/$CoCl_2$ the films degraded rapidly compared to PBS alone or with lipase. The polyurethane membrane loaded with the antibiotic tetracycline, demonstrated prolonged release over 200 h, suggesting that the polymers could be used as an implant coating for controlled drug release.

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1. Introduction

Microspheres of polycaprolactone (PCL) and its copolymers are widely used in biomedical applications, especially in drug delivery, due to their excellent biodegradability, biocompatibility and drug releasing ability [1–2]. Many different types of PCL copolymers can be made including PCL homopolymers, PCL based amphiphilic copolymers, and polymers where PCL is used as a soft segment of a polyurethane. PCL homopolymers are a family of commonly used drug carriers, typically synthesized via ring-opening polymerization of ε-caprolactone (ε-CL) catalyzed by various initiators [3], however PCL homopolymers degrade very slowly under aqueous conditions due to their hydrophobicity which offers poor water permeation abilities. Modification of PCL to improve its water affinity and degradation rate can be achieved using PEG segments [4]. PCL based amphiphilic block copolymers typically display better water compatibilities than PCL homopolymers and can be prepared by conjugation with hydrophilic materials such as polyethylene glycol or polyacrylates [5]. These PCL amphiphilic copolymers are versatile building blocks that can be used to make a variety of multifunctional polymeric materials which can self-assemble into nano structures such as vesicles and micelles [6,7] as well as microspheres [8]. Upon incorporation of these functional groups polymers have been shown to be responsive to environmental stimuli such as temperature [9,10], pH [11,12], and reduction [13,14]. They can form matrices such as films, fibers and scaffolds for drug release [15] as well as injectable or oral vessels for controlled targeted drug delivery [16]. PCL polymers have also been used as soft segments in polyurethanes that have been used in drug delivery due to their non-toxic degradation products. Thus ophylline was encapsulated, for controlled drug release, within polyurethane microspheres composed of PCL and starch as the soft segments, with 4,4′-diphenylmethane diisocyanate (MDI) and 1,4-butanediol as the hard segments [17] with drug release dependent on the dissolution and diffusion of the drug as well as degradation of the polymer.

Biomaterials play an important role in many medical devices including as coatings for urinary catheters, or other implant devices, where they need to display both biocompatibility and anti-bacterial abilities. To generate anti-bacterial capability polymeric medical devices have incorporated many features, including metal ions (e.g. Ag^+), quaternary ammonium salts, antibiotics or PEG. Antibacterial polyurethane-based materials have been used as coatings for implant devices to increase biocompatibility and reduce inflammation. Basak [18,19] developed porous polyurethane films (using poly(ether-ester) diols obtained by reacting PEG400 with lactate and 2,4-toluene diisocyanate (TDI)) loaded with antibiotics (such as rifampicin, gentamicin and ciprofloxacin). The primarily release mechanism for the hydrophilic drugs being mainly related to diffusion while the release of lipophilic drugs was controlled mainly by polymer degradation.

Mândru [20] synthesized a poly(ester-ether urethane) using poly(butylene adipate) diol and PEG as soft segments and MDI together with 1,4-butanediol (BDO) as hard segments, from which the antibiotic

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rifampicin was released in a controlled manner depending on the density of urethane groups in the polymer chains as well as the surface morphology of the polyurethane membranes.

Here polyurethane acrylates that contained as a soft segment a block copolymer of polycaprolactone-poly(ethylene glycol)-polycaprolactone (PCL-PEG-PCL) were investigated as a biodegradable drug release vehicle. Polymers of differing composition were synthesized by ring-opening polymerization of ε-caprolactone in the presence of PEG400 which was subsequently reacted with diisocyanates followed by hydroxylethyl methacrylates to give polyurethane acrylates (PUAs). By UV-curing the PUAs were polymerized to form cross-linked elastomers. Their properties and drug release profile from the cross-linked PUAs were studied.

2. Materials and methods

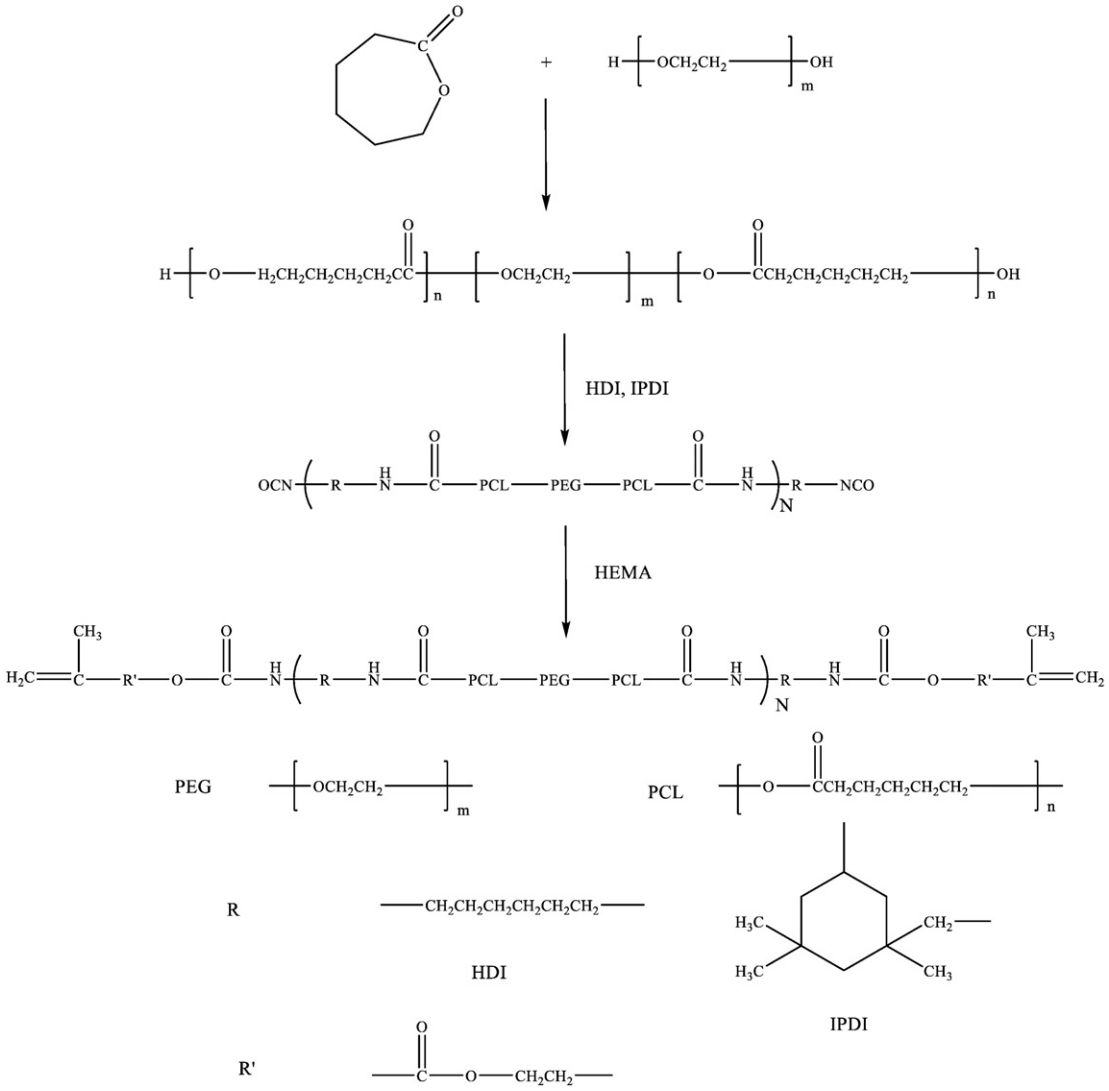
2.1. Materials

1,6-Hexamethylene diisocyanate (HDI), isophorone diisocyanate (IPDI) and hydroxylethyl methylacrylate (HEMA) were purchased from Aladdin. ε-Caprolactone, was bought from Heowns Biochem Technologies LLC,and dried with CaH_2 for 24 h at room temperature and then distilled under vacuum before use. A solution of organo-bismuth (20%) was purchased from Xianju Fusheng Compound Material Co. Ltd. PEG (M_w400), from Shanghai Ling feng Reagent Co. Ltd., was dried at 100 °C under vacuum for 2 h to remove residual water before use. Stannous octoate ($Sn(Oct)_2$) and 1-hydroxycyclohexyphenylketone (PI 184) were obtained from Sinopharm Chemical Reagent Co. Ltd. Toluene was dried by stirring with CaH_2 for 24 h before distillation and stored over 4 Å molecular sieves. The broad-spectrum antibiotic tetracycline (as the drug model) was purchased from Energy Chemical. All reagents were used as received unless mentioned otherwise. The UV lamp (model SB-100P/FA (100 w)) was from Westbury, USA.

2.2. Methods

2.2.1. Synthesis of polycaprolactone-poly(ethylene glycol)-polycaprolactone block copolymer (PdiolX)

The triblock copolymer diols (Scheme 1 and Fig. 1) were synthesized using PEG (M_w400, 5 g) to initiate the polymerization of ε-caprolactone (20 g) with $Sn(Oct)_2$ (0.3 wt%) as a catalyst in toluene (1 mL) at 130 °C for 24 h under stirring to obtain the triblock copolymers. To synthesize the copolymer diols with various molecular weights, the following molar ratios of PEG400 and ε-caprolactone were used (1/5, 1/14, 1/23) [21]. These ratios were used to control the molecular weight of the soft segment (polymer diol) keeping it between 1000 and 3000 Da.



Scheme 1. Synthesis of the polyurethane acrylate oligomers.

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