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Synthesis and water-swelling of thermo-responsive poly(ester urethane)s containing poly(ε-caprolactone), poly(ethylene glycol) and poly(propylene glycol)

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ABSTRACT

Thermo-responsive multiblock poly(ester urethane)s comprising poly(ε-caprolactone) (PCL), poly(ethylene glycol) (PEG), and poly(propylene glycol) (PPG) segments were synthesized. The copolymers were characterized by GPC, NMR, FTIR, XRD, DSC and TGA. Water-swelling analysis carried out at different temperatures revealed that the bulk hydrophilicity of the copolymers could be controlled either by adjusting the composition of the copolymer or by changing the temperature of the environment. These thermo-responsive copolymer films formed highly swollen hydrogel-like materials when soaked in cold water and shrank when soaked in warm water. The changes are reversible. The mechanical properties of the copolymer films were assessed by tensile strength measurement. These copolymers were ductile when compared to PCL homopolymers. Young's modulus and the stress at break increased with increasing PCL content, whereas the strain at break increased with increasing PEG content. The results of the cytotoxicity tests based on the ISO 10993-5 protocol demonstrated that the copolymers were non-cytotoxic and could be potentially used in biomedical applications.

1. Introduction

In the field of biomaterials, there is great interest in the development of degradable materials. Synthetic biodegradable polymers can be used as materials for temporary scaffolds for tissue engineering purposes, as sutures, drug delivery devices, orthopedic fixation devices or temporary vascular grafts. These polymers need to possess the desired biocompatibility, suitable mechanical properties and predictable biodegradability. For application in the body, materials with a high water affinity offer the added advantage of compatibility with the internal environment of the body, which has high water content. Hydrogels are such materials and are the first materials to be developed for application in the human body [1,2]. There are three classes of hydrogels: (i) chemical crosslinked, (ii) physical crosslinked and (iii) 'pulley' gels. Chemically crosslinked hydrogels are formed by the copolymerization of a monomer having one polymerizable double bond with a crosslinking agent having at least two polymerizable double bonds. Physical hydrogels are self-assembled three-dimensional structures which are held together by non-covalent junctions, these include Coulombic, dipole–dipole, van der Waals, hydrophobic, and hydrogen bonding interactions [3–5]. The latest addition to the family of hydrogels is a class of hydrogels known as 'pulley' gels [6]. By chemically crosslinking two cyclodextrin molecules, each threaded on a different poly(ethylene glycol) (PEG) chain that is end-capped with a bulky group, a sliding double ring crosslinking agent was produced. These topologically crosslinked gels possess sliding crosslinks and have been demonstrated to have excellent swellability [6].

Our work focuses on the synthesis of water swellable thermo-responsive hydrogel-like materials. The main mode of crosslinking is by physical interactions between the hydrophobic segments and does not rely on toxic crosslinking agents to form a hydrogel. An added advantage is that, unlike crosslinked hydrogels, this copolymer is solution-processable and can be applied as thin film 'smart' coatings. This material is water-insoluble and shows stability in large amounts of water that other thermogelling copolymers do not. This work focuses on the synthesis of a copolymer incorporating three materials which are widely regarded as candidate materials for biomedical applications. They are poly(ethylene glycol) (PEG), poly(propylene glycol) (PPG) and poly(ε-caprolactone) (PCL). These materials are linked to form linear multiblock poly(ester urethane)s. Polyurethanes are widely applied in various biomedical applications such as heart valves [7], dialysis membranes [8] and pacing leads insulation [9,10]. Moreover, polyurethanes have good elastic properties due to the hydrogen bonding between the urethane bonds, making them attractive for applications where elasticity is required, such as

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ligament tissue engineering [11–13]. However, polyurethanes have been reported to undergo slow hydrolytic degradation [14]. In order to render the polyurethanes more hydrolytically degradable, biodegradable hard segments such as poly[(R)-3-hydroxybutyrate] (PHB) have been introduced into the polyurethane backbone to form poly(ester urethane)s [15,16]. These poly(ester urethane)s have been shown to degrade within two weeks under accelerated hydrolytic degradation conditions [17].

PCL is a biocompatible polyester which has been extensively investigated for use as a biomedical material. The degradation product of PCL is 6-hydroxyhexanoic acid, which is a naturally occurring metabolite in the human body. Sutures having PCL as a main component have been approved by the Food and Drug Administration (FDA) for use in surgeries, attesting to its safe application in humans [18–20]. In other applications, PCL is used in Capronor, a commercially available 1-year implantable contraceptive device [21]. The toxicology of poly(ε-caprolactone) has been thoroughly studied in the safety evaluation of Capronor and the material has been generally regarded as safe.

On the other hand, Pluronics or the PEG–PPG–PEG triblock copolymer is a well known FDA approved polymer and has been applied in drug delivery systems as a thermogelling system [22,23]. The main reason for the thermosensitivity is due to the presence of the PPG block in the polymer. PPG is water-soluble at low temperatures and reverts into the insoluble form at higher temperatures [24]. This behavior is similar to the behavior of poly(*N*-isopropyl acrylamide) (PNIPAAm), another extensively studied 'smart' polymer. Smart hydrogels comprising PNIPAAm have been synthesized for various applications and these gels respond to external stimuli, such as temperature [25–28]. When the temperature is raised, the gel shrinks, expelling its contents. When the temperature is lowered, the gel swells, absorbing the fluid from its external environment. However, safety concerns remain over the use of PNIPAAm in materials for biomedical applications due to the possible presence of the monomeric acrylamide-based residues, which is a neurotoxin [29,30].

This paper will highlight on the synthesis and the characterization of a new class of poly(ester urethane)s comprising PEG, PPG and PCL. This material forms a hydrogel-like material when it absorbs water and does not require the use of toxic crosslinking agents. We demonstrate for the first time, the reversible cyclical thermo-responsive behavior of this 'smart' material. The promising results shown by this new material make it a highly attractive candidate for use in biomedical devices that require regulation of behavior by temperature control.

2. Experimental section

2.1. Materials

Poly(ethylene glycol) (PEG) with M_n of ca. 2000 and poly(propylene glycol) (PPG) and poly(ε-caprolactone)-diol (PCL-diol) with M_n of ca. 1000 were purchased from Aldrich. Purification of the PEG was performed by dissolving in dichloromethane followed by precipitation in diethyl ether and vacuum-dried before use. Purification of PPG was performed by washing in hexane three times and vacuum-drying before use. The M_n and M_w of PEG were found to be 1890 and 2060, respectively. The M_n and M_w of PPG were found to be 780 and 990, respectively. The M_n and M_w of PCL-diol were found to be 1040 and 2320, respectively. Dibutyltin dilaurate (95%), 1,6-hexamethylene diisocyanate (HMDI) (98%), methanol, diethyl ether and 1,2-dichloroethane (99.8%) were purchased from Aldrich. 1,2-Dichloroethane was distilled over CaH_2 before use.

2.2. Synthesis of poly(PEG/PPG/PCL urethane)s

Poly(PEG/PPG/PCL urethane)s were synthesized from PEG, PPG and PCL-diol using HMDI as a coupling reagent. The amount of HMDI added was equivalent to the reactive hydroxyl groups in the solution. Typically, 4 g of PCL-diol ($M_n = 1040$, 3.85×10^{-3} mol), 4 g of PEG ($M_n = 1890$, 2.12×10^{-3} mol), and 2 g of PPG ($M_n = 780$, 2.56×10^{-3} mol) were dried in a 250-mL two-neck flask at 50 °C under high vacuum overnight. Then, 200 mL of anhydrous 1,2-dichloroethane was added to the flask, and any trace of water in the system was removed through azeotropic distillation with only 20 mL of 1,2-dichloroethane being left in the flask. When the flask was cooled down to 75 °C, 1.43 g of HMDI (8.53×10^{-3} mol) and two drops of dibutyltin dilaurate ($\sim 8 \times 10^{-3}$ g) were added sequentially. The reaction mixture was stirred at 75 °C under a nitrogen atmosphere for 48 h. The resultant copolymer was precipitated from diethyl ether and further purified by redissolving into 1,2-dichloroethane followed by precipitation in a mixture of methanol and diethyl ether to remove remaining dibutyltin dilaurate. A series of poly(PEG/PPG/PCL urethane)s with different PCL content were prepared, and their number-average molecular weight and polydispersity values are given in Table 1. The yield was 80% and above after isolation and purification.

^{1}H NMR ($CDCl_3$) of poly(PEG/PPG/PCL urethane), EPC3: δ (ppm) 1.09 (O(CH_3)$CHCH_2O$), 1.29 ($OCH_2CH_2CH_2CH_2CH_2CO$), 1.47 ($OOCNHCH_2CH_2CH_2CH_2CH_2CH_2NHCOO$), 1.60 ($OCH_2CH_2CH_2CH_2CH_2CO$), 2.26 ($OCH_2CH_2CH_2CH_2CH_2CO$), 3.15 ($OOCNHCH_2CH_2CH_2CH_2CH_2CH_2NHCOO$), 3.42 (O($CH_3$)$CHCH_2O$), 3.47 (O($CH_3$)$CHCH_2O$), 3.64 ($OCH_2CH_2O$), 4.02 ($OCH_2CH_2CH_2CH_2CH_2CO$), 4.21 ($OOCNHCH_2CH_2CH_2CH_2CH_2CH_2NHCOO$).

^{13}C NMR ($CDCl_3$) of poly(PEG/PPG/PCL urethane), EPC3: δ (ppm) 17.68 (O(CH_3)$CHCH_2O$), 24.93 ($OCH_2CH_2CH_2CH_2CH_2CO$), 25.89 ($OCH_2CH_2CH_2CH_2CH_2CO$), 26.66 ($OOCNHCH_2CH_2CH_2CH_2CH_2CH_2NHCOO$), 28.17 ($OCH_2CH_2CH_2CH_2CH_2CO$), 30.28 ($OOCNHCH_2CH_2CH_2CH_2CH_2CH_2NHCOO$), 34.48 ($OCH_2CH_2CH_2CH_2CH_2CO$), 41.32 ($OOCNHCH_2CH_2CH_2CH_2CH_2CH_2NHCOO$), 64.47 ($OCH_2CH_2CH_2CH_2CH_2CO$), 70.89 ($OCH_2CH_2O$), 73.65 (O($CH_3$)$CHCH_2O$), 75.82 (O($CH_3$)$CHCH_2O$), 156.76 ($OOCNHCH_2CH_2CH_2CH_2CH_2CH_2NHCOO$), 173.83 ($OCH_2CH_2CH_2CH_2CH_2CO$).

2.3. Molecular characterization

Gel permeation chromatography (GPC) analysis was carried out with a Shimadzu SCL-10A and LC-8A system equipped with two Phenogel 5μ 50 and 1000 Å columns (size: 300 × 4.6 mm) in series and a Shimadzu RID-10A refractive index detector. Tetrahydrofuran (THF) was used as eluent at a flow rate of 0.30 mL min^{-1} at 45 °C. Monodispersed poly(ethylene glycol) standards were used to obtain a calibration curve. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AV-400 NMR spectrometer at room temperature. The ^{1}H NMR measurements were carried out with an acquisition time of 3.2 s, a pulse repetition time of 2.0 s, a 30° pulse width, 5208 Hz spectral width, and 32 K data points. Chemical shift was referred to the solvent peaks ($\delta = 7.3$ ppm for $CHCl_3$). Fourier transform infrared (FTIR) spectra of the polymer films coated on CaF_2 plates were recorded on a Bio-Rad 165 FTIR spectrophotometer; 64 scans were signal-averaged with a resolution of 2 cm^{-1} at room temperature.

2.4. Thermal analysis

Thermogravimetric analyses (TGA) were carried out on a TA Instruments SDT 2960. Samples were heated at 20 °C min^{-1} from room temperature to 800 °C in

Table 1
Molecular characteristics of poly(PEG/PPG/PCL urethane)s

Copolymer[a]	Feed ratio (wt%)			Composition in copolymer (wt%)[c]			Composition in copolymer (wt%)[d]		Copolymer characteristics		
	PEG	PPG	PCL	PEG	PPG	PCL	PPG + PCL	PEG	M_n[b] (×10^3)	M_w/M_n[b]	T_g (°C)
EPC1	50.0	25.0	25.0	52.7	22.0	25.4	45.6	54.4	68.1	1.91	−46.3
EPC2	40.0	20.0	40.0	44.2	17.1	38.7	57.2	42.8	71.2	1.89	−54.2
EPC3	28.6	14.3	57.1	32.6	12.1	55.3	71.5	28.5	64.1	1.90	−57.5
EPC4	18.2	9.1	72.7	20.3	8.6	71.1	80.2	19.8	66.5	1.89	−58.9

[a] Poly(PEG/PPG/PCL urethane)s are denoted EPC, E for PEG, P for PPG and C for PCL. The M_n of PEG and PPG used for the copolymer synthesis was 1890 and 780 g mol^{-1}, respectively.
[b] Determined by GPC.
[c] Calculated from ^{1}H NMR results.
[d] Calculated from TGA results.