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Preparation and Cytotoxicity of Novel Aliphatic Polycarbonate Synthesized from Dihydroxyacetone

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Abstract: A new cyclic carbonate, 2,2-ethylenedioxypropane-1,3-diol carbonate (EOPDC), was synthesized through a two-step reaction from dihydroxyacetone dimer, and polymerized in bulk initiated by $Sn(Oct)_2$ to give a high molecular weight polycarbonate. The structure of monomer and the polymer were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR. The cytotoxicity of the obtained polycarbonate was investigated by MTT assay.

Keywords: Ring-opening polymerization, aliphatic polycarbonate, cytotoxicity.

Aliphatic polycarbonates represent one family of bioresorbable materials used for biomedical applications such as drug delivery carrier and implant materials because of their good biocompatibility, low toxicity, and biodegradability[1]. Recently, increasing attention has been paid to the synthetic aliphatic polycarbonates bearing functional groups including alkyl, OH, NH_2, COOH, and COOR, because these functional groups can be used to regulate the hydrophilicity/hydrophobicity, permeability, bioresorption and mechanical properties[2-5].

In our pervious study, we prepared a novel biodegradable aliphatic polycarbonate, poly(2,2-ethylenedioxypropane-1,3-diol carbonate)(PEOPDC), based on dihydroxyacetone with ethylene ketal protected carbonyl group[6]. The novel polycarbonate was obtained by the ring-opening polymerization of six-membered cyclic carbonate monomer, 2,2-ethylenedioxypropane-1,3-diol carbonate (EOPDC). Compared with poly (2, 2-dimethyltrimethyl carbonate) (PDTC), PEOPDC has a higher glass-transition temperature (T_g = 49°C), and a higher rate of hydrolytic degradation.

In this study, EOPDC was prepared through a simplified synthetic pathway and polymerized in bulk initiated by $Sn(Oct)_2$ at 110°C to give the polycarbonate. The cytotoxicity of the obtained polycarbonate was evaluated by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay[7].

Monomer EOPDC can be obtained by a four-step reaction starting from diethyl malonate in our previous paper[6]. In this investigation, we synthesized this monomer by

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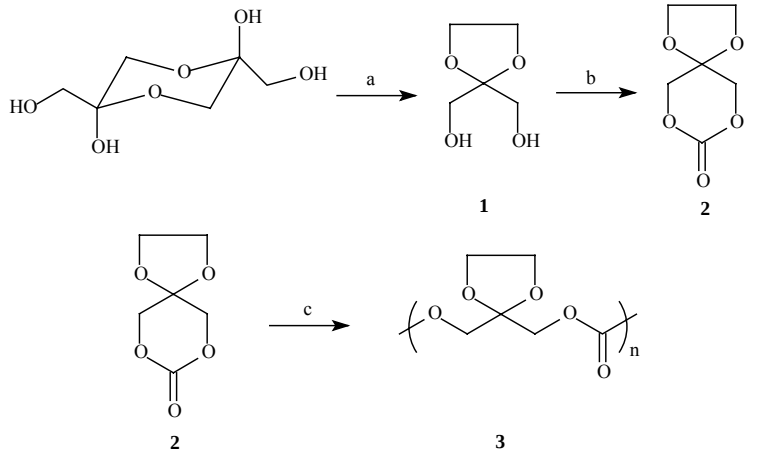
a novel two-step reaction starting from dihydroxyacetone dimmer. The synthesis of EOPDC is shown in **Scheme 1**. Dihydroxyacetone dimmer reacted with glycol in the presence of *p*-toluenesulfonic acid as catalyst to give **1** (1, 3-dioxolan-2, 2-dimethanol) with the yield of 10%. The low yield was due to the dehydrate reaction of dihydroxyacetone dimmer catalyzed by the acid during the reaction[8]. Then the cyclic carbonate monomer (EOPDC) **2** was obtained in 40% yield by treating **1** with triphosgene using a modified method as described in literature[9].

Monomer **2** proceeded ring-opening polymerization to obtain the polycarbonate (PEOPDC) **3** in bulk using $Sn(Oct)_2$ as an initiator[6]. According to our pervious study, the optimized polymerization conditions were at 110ºC for 12 h with a ratio of monomer/initiator 1000. The *Mn* of the resulting polycarbonate was 55000 with polydispersity of 1.46. The chemical structures of monomer and polymer were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR[10].

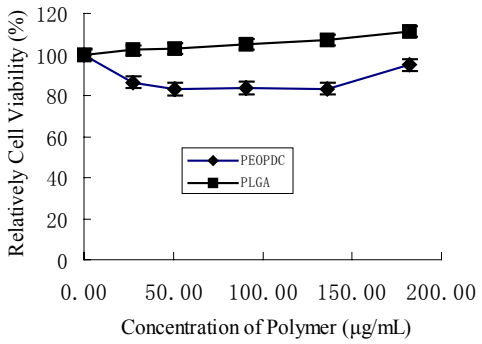
The *in vitro* cytotoxicity of the novel polycarbonate (PEOPDC) **3** was evaluated by using the MTT assay. Because poly[(lactic acid)-co-(glycolic acid)] (PLGA) has been approved by the Food and Drug Administration (FDA) for biomedical applications, in this study, we evaluated the cytotoxicity of PEOPDC using commercially available PLGA (75:25) as a control[7]. The result showed that the cytotoxicity of PEOPDC was a little bit higher than that of PLGA. However, the value was still in a low cytotoxicity range (**Figure 1**), indicating PEOPDC was expected to have promising applications in biomedical fields such as drug controlled release system, implant materials and tissue engineering.

Scheme 1 The synthetic pathway of polycarbonate



Reaction conditions: a: glycol, *p*-toluenesulfonic acid, benzene, reflux, yield: 10%;
b: dichloromethane, triphosgene, pyridine, yield: 40%;
c: Sn(Oct), 110°C, in bulk, yield: 92.6%

Figure 1 *In vitro* cytotoxicity of PEOPDC



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10. Characterization results of the monomer and the polymer are as follows. **2**: IR (KBr, ν cm^{-1}): 1751.9 (C=O), 1183.8, 1095.7, 1131.3 (C-O-C): ^{1}H NMR (300MHz, $CDCl_3$, δ ppm): 4.239 (s, 4H, CH_2OCOCH_2), 4.049 (s, 4H, OCH_2CH_2O); ^{13}C NMR (300MHz, $CDCl_3$, δ ppm): 147.136 (C=O), 99.474 (tetrasubstituted C), 70.730 (CH_2OCOCH_2), 64.898 (OCH_2CH_2O). **3**: IR (KBr，ν cm^{-1}): 1758.7 (C=O), 1255.3, 1181.9, 1043.0 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.181 (s, 4H, CH_2OCOCH_2), 4.012 (s, 4H, OCH_2CH_2O); ^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 153.120 (C=O), 104.601 (tetrasubstituted C), 66.242 (CH_2OCOCH_2), 65.420 (OCH_2CH_2O).

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