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Hydrolytically degradable poly(ethylene glycol) based polycarbonates by organocatalyzed condensation

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ABSTRACT

Poly(ethylene glycol) is one of the most used stealth polymer in the field of polymer-based drug delivery. In spite of its excellent biocompatibility, high molecular poly(ethylene glycol) can be accumulated in the body, in contrast to low molar mass one. This is due to the non-degradability of poly(ethylene glycol) which can cause some negative side effects. In order to overcome this drawback, in this work we present new degradable high molecular poly(ethylene glycol) by simply incorporating carbonate groups between poly(ethylene glycol) units. Thus, poly(ethylene glycol) based polycarbonates have been synthesized by polycondensation of dimethyl carbonate and poly(ethylene glycol) of four different low molar masses; 600, 1000, 1500 and 2000 g mol^{-1}. Optimum bulk polycondensation reactions were run in two steps in the presence of 4-dimethylaminopyridine organocatalyst. By this method, poly(ethylene glycol) based polycarbonates were prepared and characterized showing molar masses between 10 and 35 kg mol^{-1} and crystallinity was increased compared to the initial low molar mass poly(ethylene glycol)s. The hydrolytic degradation of the poly(ethylene glycol) based polycarbonates was investigated *in vitro* using a phosphate buffer solution at pH = 7.2. The results showed that the initial poly(ethylene glycol)-polycarbonates hydrolyzed by the carbonate units showing a decrease of molar mass as a function of time. It was found that all polycarbonates underwent almost complete hydrolysis after 50 days leading to the initial low molar mass poly(ethylene glycol) units that are bellow renal clearance threshold.

1. Introduction

The use of polymers in biomedical applications is continuously increasing [1–3]. In spite of the recent development, poly(ethylene glycol) (PEG) is still one of the most preferable candidate [4,5]. Properties, such as the hydrophyilicity, biocompatibility and its low interaction with the blood components, make PEG one of the best option for bio-applications [6]. In addition, PEG has been already approved by the Food and Drug Administration (FDA) which facilitates the commercialization of PEG based products. PEG is the most employed polymer when we referred to the stealth polymers and it has been widely used to transport drugs, gene or a protein through the blood due to its excellent circulation time and biocompatibility. Moreover, PEG is capable to transport the compound before being recognized by the immunologic system.

It has been reported that high molar mass polymers is the best scenario for biomedical applications [6], as in these conditions the renal clearance is diminished and the long term stability is augmented [1,2,7–11]. Consequently, high molar mass PEG leads to increase the capability of targeting the desired properties owing to longer residence time *in vivo*. Moreover, several studies have

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demonstrated that the toxicity of PEG is inversely proportional to the molar mass, decreasing the *in vivo* cytotoxicity increasing the molar mass [12,13]. Although there are many advantages about using PEG, there are also drawbacks. The most apparent disadvantage of PEG is the lack of degradability and can be accumulated *in vivo* after finishing its function. Therefore, there are different solutions to overcome the problem. Recently, it has been demonstrated the possibility of a slow biodegradation of PEG by oxidative degradation under biologically significant conditions [14]. However, when faster degradability of the polymer is desired the design of new polymers is required. As a partial solution, block copolymers can be synthesized, having PEG as non-degradable block, and polylactic acid [15] or polycaprolactone [16] as degradable block. On the other hand, high molar mass PEG with hydrolysable linkages within the polymer structure will also facilitate its clearance from the body [17].

The generation with degradable linkages has given several alternatives on the design of PEG based degradable polymers. For instance, esters [18,19], urethanes [20–22], disulfides [23] and thiols [24,25] are some of the functional groups that have been incorporated so far to induce degradability to PEG based polymers. Thus, the polymer will possess high molar mass favouring the targeting and at the same time will have the potential to degrade *in vivo* after completing the function. Depending on the moiety introduced to PEG, the degradation mechanism and time will be different. Moreover, the incorporated degradable linkages can generate some side products upon degradation, conditioning the application and the effectiveness of the polymer.

In the last decade, one of the polymer families that have received considerable attention is aliphatic polycarbonates, because of their low toxicity, biocompatibility and degradability. In addition after degrading, carbonates mainly release water and CO_2, which reduces the potential to induce any extra toxicity related to the incorporation of this degradable backbone. Regarding the literature, 2 main polymerizations are explored to synthesize polycarbonates: (i) ring opening polymerization of cyclic carbonates [26,27] and (ii) polycondensation between dimethyl carbonate and a diol [28,29]. In the last route, dimethyl carbonate is polymerized by step growth polymerization with a diol in the presence of a catalyst. Consequently, a carbonate bond is generated in the polymer backbone. Different types of catalysts have been investigated for the polycondensation of dimethyl carbonate with diols [28,30,31]. Although transition metal catalysts have proven very reliable and efficacious, for nanomedicine they are not considered as the best choice due to the difficulties in removing. This fact can generate some toxicity due to the presence of residual catalyst moieties. Besides, organo-mediated catalysts have shown to be in some cases less toxic and they can efficiently replaced metal catalyst in some polymerizations [32]. One appropriate candidate for this kind of polymerization is 4-dimethylaminopyridine (DMAP) which gives low toxicity in human cells when it is used in low amounts [33].

In this work we have synthesized PEG based polycarbonates by polycondensation of dimethyl carbonate and poly(ethylene glycol) of four different molar masses 600, 1000, 1500 and 2000 g mol^{-1} using DMAP organocatalyst. First, the best conditions to perform the polymerization have been studied and after, the degradability of these systems *in vitro* has been investigated.

2. Materials and methods

2.1. Materials

Dry dimethyl carbonate (DMC) (99+ %, extra dry), organocatalyst 4-dimethylaminopyridine (DMAP) (99%) and poly(ethylene glycol)s (PEGs) with different molar masses, 600 g mol^{-1}, 1000 g mol^{-1}, 1500 g mol^{-1} and 2000 g mol^{-1} were purchased from Across Organics. Solvents tetrahydrofurane (GPC grade) was obtained from Scharlab, dichloromethane (DCM) (Certified AR for Analysis), diethyl ether (Certified AR for Analysis) from Fisher Scientific and deuterated chloroform (99.8%) from Deutero GmbH. Phosphate Buffered Saline System (PBS) was supplied by Sigma-Aldrich. All PEGs were dried by azeotropic distillation (60 °C) in toluene for 8 h and DMAP was dried for 8 h at room temperature prior to use.

2.2. Synthetic route

Polymers with different ethylene oxide units were synthesized by polycondensation in 2 step reaction. The optimal molar ratio between DMC/diol/catalyst was found to be 8:1:0.01. DMC (8 equiv., 6.7 mL, 0.08 mol), PEG 600 g mol^{-1} (1 equiv., 6 g, 0.01 mol) and an organocatalyst DMAP (0.01 equiv., 0.012 g, 0.1 mmol) were added into a round bottom two necked flask, where the flask was connected to the vacuum, in inert atmosphere, totally excluded from water. In the first step, the temperature was raised stepwise and kept isothermally at 130 °C for 7 h. During the second step, the temperature was increased until 180 °C and high vacuum (0.5 mbar) was applied. The reaction was left running overnight. The resulting polymer was first dissolved in dichloromethane and then precipitated, pouring the polymer into solution into an excess of cold diethyl ether, obtaining white powder in 80–95% yield. The polymer was characterized by ^{1}H NMR and ^{13}C NMR: PC-PEG600: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.28 (t, OCOOC$\boldsymbol{H_2}$, 4H), 3.72 (t, OCOOCH$_2$C$\boldsymbol{H_2}$, 4H), 3.64 (s, OC$\boldsymbol{H_2}$, 44H) ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.26 (O$\boldsymbol{C}$OO), 70.70 (O$\boldsymbol{C}$H$_2$), 69.02 (OCOOCH$_2$$\boldsymbol{C}H_2$), 67.17 (OCO$\boldsymbol{C}H_2CH_2$).

2.3. Characterization methods

Proton and carbon nuclear magnetic resonance spectra were obtained in a Bruker AVance DPX 500 MHz. All the spectra were recorded at room temperature in a chloroform solution.

Molar mass distributions of polymers were measured by size exclusion chromatography (SEC). Samples were diluted in THF (GPC grade) to a concentration of approximately 5 mg mL^{-1} and filtered through a 0.45mm nylon filter. The SEC set up consisted of a pump (LC-20A, Shimadzu), an autosampler (Waters 717), a differential refractometer (Waters 2410) and three columns in series