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Emulsifying properties and degradation characteristics of bioresorbable polymeric emulsifiers in aqueous solution and oil-in-water emulsion

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ABSTRACT

Three amphiphilic bioresorbable copolymers derived from lactide (LA), ε-caprolatcone (CL) and poly(-ethylene glycol) (PEG) were investigated for their emulsifying properties and degradation characteristics. Polymers consisted of 80 wt% hydrophilic PEG block and 20 wt% lipophilic PLA, PCL, PLACL block were synthesized by ring-opening polymerization of LA and/or CL in the presence of monomethoxy PEG. By possessing similar hydrophilic-lipophilic balance (HLB) values, these polymeric emulsifiers have an equivalent ability to stabilize squalane/water interfaces during emulsification. Degradation of polymers in aqueous solution and within emulsion was carried out in water at 37 °C selected to mimic the human body conditions. Our results demonstrated that the degradability intrinsic to each polymer is the predominant cause of destroying the emulsion. Moreover, polymer matrices within the emulsion exhibited lower degradation rates than the corresponding polymers in aqueous solution. These features are of great interest in pharmaceutical applications, especially for the design of sustained delivery systems.

1. Introduction

Amphiphilic bioresorbable polymers, in particular those derived from poly(ethylene glycol) (PEG), polylactide (PLA), and poly(ε-caprolatcone) (PCL), have attracted substantial attention for sustained delivery of biologically active agents due to their outstanding biocompatibility and bioresorbability [1–4]. Studies have investigated the sustained delivery of self-assembled vehicles with enhanced therapeutic efficacy for a wide variety of anticancer agents, such as hydrogels for the permeation and retention of short-lived cisplatin in the circulation [5], as micelles for the solubilization and stabilization of lipophilic paclitaxel [6], and as micro/nanoparticles for the reduction of side effects of irritant doxorubicin [7].

Oil-in-water (O/W) emulsions, which are elaborated by hydrophilic emulsifiers, are oil droplets dispersed into a continuous water phase [8,9]. In pharmaceutics, this type of delivery system is known as an effective carrier in applications for the delivery of the anticancer drug paclitaxel [8]. In vaccine formulations, O/W was successfully applied as vaccine adjuvants for antigen sparing in pandemic influenza vaccine preparedness and for enhancing the immunogenicity of seasonal influenza vaccines in elderly persons [9]. Our research group was the pioneer who investigates the use of amphiphilic bioresorbable polymers as hydrophilic emulsifiers to stabilize oily/aqueous interfaces and thereby yield isotropic emulsions with high affinity to water [10,11]. Ideally, the polymeric emulsifier can stabilize the emulsion during preparation and storage. Following administration, the emulsified particles work as delivery vehicles (as depots/carriers) in order to either adsorb or encapsulate the bioactive agents, thus effectively manipulating their bioavailability. Then, the degradable nature of the polymers predominates that the emulsion being destroyed and further absorbed *in vivo* [10]. Therefore, these bioresorbable polymers could enlarge the selection of emulsifiers for the design of a new generation of emulsion formulations. Immunogenicity studies in mice have also demonstrated the potential of this type of emulsion as adjuvants for the development of prophylactic vaccines against emerging infectious diseases as well as sustained delivery of tumor-associated antigens against cancers [12,13]. Despite what has been achieved to date, a complete understanding of whether the presence of oil in the polymeric aqueous solution can affect the

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hydrolytic cleavage of the main chain polymer remains unclear. This feature is important to predict the hydrolytic degradation rate *in vivo*. Moreover, it is also interesting to know how the degradation characteristics of each polymeric emulsifier are involved with the disintegration of the emulsions.

In this work, we investigate the hydrolytic degradation of diblock bioresorbable polymers, namely, poly(ethylene glycol)-*block*-polylactide (PEG-*b*-PLA), poly(ethylene glycol)-*block*-poly(ε-caprolactone) (PEG-*b*-PCL), and poly(ethylene glycol)-*block*-poly(-lactide-co-ε-caprolactone) (PEG-*b*-PLACL) in aqueous solutions or within emulsions, with the aim of elucidating the *in vivo* behavior of these polymeric emulsifiers and understanding the contribution of the LA and CL segments during degradation (Fig. 1). Moreover, we investigate how the degradation properties of the polymeric emulsifier can affect the stability of the resulting emulsion. Degradation was carried out in water at 37 °C to mimic *in vivo* conditions and was followed by gel permeation chromatography (GPC).

2. Materials and methods

2.1. Materials

DL-lactide was purchased from Aldrich (Seelze, Germany) and recrystallized from acetone. Polyethylene glycol 5000 monomethyl ether ($MePEG_{5000}$) was supplied by Fluka (Buchs, Switzerland) and used as received. Tin(II) 2-ethylhexanoate ($SnOct_2$), phosphate buffer saline (PBS), squalane, and dimethyl sulfoxide-d_6 (DMSO-d_6) were purchased from Sigma (St. Louis, Missouri, USA). All solvents were of analytical grade. AB-type diblock copolymer PEG-*b*-PLACL was synthesized by ring-opening polymerization of DL-lactide and ε-caprolatcone in the presence of $MePEG_{5000}$ and $SnOct_2$, as described previously [14]. PEG-*b*-PLA and PEG-*b*-PCL were synthesized in the same manner with predetermined amounts of MePEG/lactide or MePEG/ε-caprolactone.

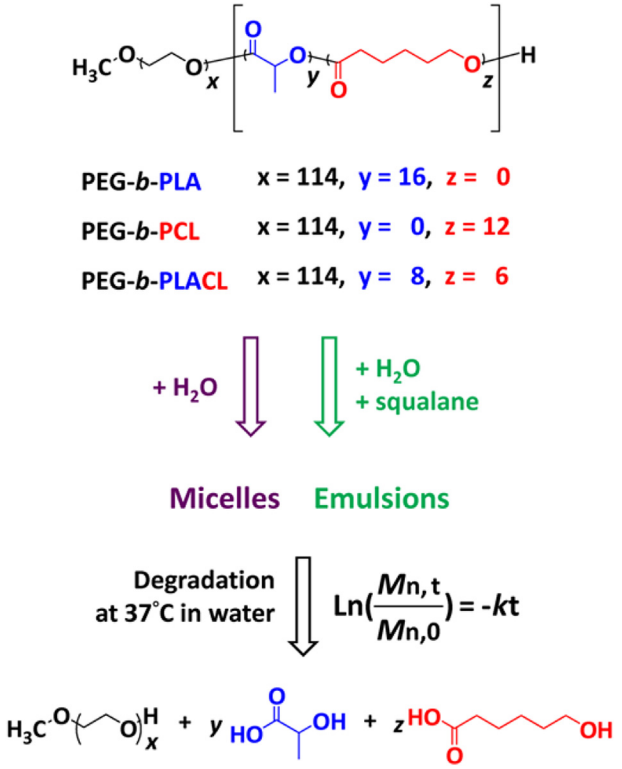

Fig. 1. Schematic representation of the hydrolytic degradation of diblock bioresorbable polymers, PEG-*b*-PLA, PEG-*b*-PCL, and PEG-*b*-PLACL in aqueous solutions or within emulsions.

2.2. Emulsion preparation

Polymer (150 mg), 0.6 mL of distilled, de-ionized water, and 1.728 mL of squalane oil were emulsified using a homogenizer at 6000 rpm for 5 min.

2.3. Hydrolytic degradation

Ten milligrams of polymer were dissolved in an Eppendorf tube filled with 100 μL of distilled, de-ionized water. Emulsion suspensions were investigated by re-dispersing 20 μL of stock emulsion into 80 μL of water. The tubes were placed in a circulating water bath at 37 °C. At predetermined time points, specimens were collected and lyophilized before being subjected to analyses. The data are expressed as the mean plus or minus the standard error of the mean.

2.4. Measurements

^{1}H NMR spectra were recorded at room temperature with a Varian VXR 300 MHz spectrometer (Varian, Palo Alto, CA, USA) using DMSO-d_6 as the solvent and tetramethylsilane (TMS) as the shift reference. GPC was performed using a setting composed of an isocratic pump, a refractive index (RI) detector, and two size exclusion columns connected in series, one PLgel 5 μm guard column (7.5 × 50 mm) and one PLgel 5 μm mixed-D column (7.5 × 300 mm). The mobile phase was tetrahydrofuran (THF), and the flow rate was 0.8 mL/min. M_n and the polydispersity (M_w/M_n) were expressed relative to polystyrene standards (Varian, Inc., Amherst, MA, USA).

3. Results and discussion

3.1. Polymers with similar HLB values have an equivalent ability to stabilize oil/water interfaces during emulsification

Table 1 shows the compositional and molecular characteristics of the bioresorbable polymeric emulsifiers considered in this study. The molar ratio of lactyl units to caproyl units to oxyethylene, or [LA]/[CL]/[OE] molar ratio, was determined from the integrations of the bands due to PLA blocks at 5.2 ppm, PCL blocks at 4.0 ppm and PEG blocks at 3.6 ppm in the ^{1}H NMR spectra, as previously described [11]. The three polymers have similar molecular characteristics of 80 wt % of hydrophilic PEG blocks and 20 wt % of

Table 1
Molecular characteristics of $MePEG_{5000}$ and its derived copolymers PEG-*b*-PLA, PEG-*b*-PCL, and PEG-*b*-PLACL.

Polymer	^{1}H NMR			GPC[d]	
	[LA]/[CL]/[OE][a]	$W_{PEG}:W_{PLA/CL}$[b]	HLB[c]	M_n	M_w/M_n
$MePEG_{5000}$	-/-/1	100:0	20.0	6550	1.07
PEG-*b*-PLA	0.139/-/1	81:19	16.2	8675	1.07
PEG-*b*-PCL	-/0.095/1	80:20	16.0	8050	1.12
PEG-*b*-PLACL	0.078/0.045/1	80:20	16.0	8400	1.06

[a] The [LA]/[CL]/[OE] molar ratio was determined from the integrations of the signals due to PLA blocks at 5.1 ppm, PCL blocks at 4.0 ppm and PEG blocks at 3.6 ppm in the ^{1}H NMR spectra.
[b] $W_{PEG}:W_{PLA/CL} = M_{n,PEG}:M_{n,PLA/CL} = 5000:(72 \times 5000/44 \times [LA]/[OE] + 114 \times 5000/44 \times [CL]/[OE])$.
[c] HLB copolymer $= 20 \times (W_{PEG}/W_{PLA/CL})$.
[d] Data obtained by GPC with respect to polystyrene standards.