

Synthesis and characterization of ABA types tri-block copolymers derived from p-dioxanone, ϵ -caprolactone and poly(ethylene glycol)

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Introduction

Colloidal system, in the form of micro- and nano- sized particle, has been frequently used in biomedical field to encapsulate hydrophobic drugs and other bioactive molecules. The fascinating aspect of this system in biomedical field is for increasing drug stability, drug solubility, and transport properties of pharmaceutical molecules[1]. Polymers containing at least two distinct blocks (hydrophobic and hydrophilic), covalently bound at one point, lead to form a polymeric nanoparticles via intra- or intermolecular associations between hydrophobic moieties in aqueous medium since this medium is thermodynamically unfavorable to the hydrophobic segment[2]. polymeric nanoparticles made up of synthetic biodegradable block copolymers have much attention due to their core-shell geometry in which core (hydrophobic domain) serves as a reservoir for the incorporated drugs and shell (hydrophilic domain) serves as a stabilizing interface of particles. The objective of this research was the synthesis of a novel amphiphilic tri-block copolymer, PPDO-co-PCL-b-PEG-b-PPDO-co-PCL, and preparation of nanoparticles in aqueous medium. The random increase in PCL on PPDO-b-PEO-PPDO could improve the flexibility and hydrophobicity of the resulting polymer consequently a novel poly (ester-alt-ether) based polymeric nanoparticles of reasonable physicochemical characteristics can be prepared.

Materials and Methods

ϵ -caprolactone (ϵ -CL), poly(ethylene glycol) (PEG) ($M_n = 10,000$), stannous 2-ethyl hexanoate [$\text{Sn}(\text{oct})_2$], (Aldrich Chemical Co.) and 1,4-dioxan-2-one (PDO), provided by Meta Biomedical Co. Ltd. Korea, were used after some purification. Polymers (PPDO-co-PCL-b-PEG-b-PPDO-co-PCL) were synthesized by the ring opening polymerization (ROP) of p-dioxanone and ϵ -caprolactone in presence of PEG and stannous octoate as a macroinitiator and catalyst, respectively[3]. Polymerization and molecular composition of the polymer was analyzed by different physico-chemical techniques ($^1\text{H-NMR}$, $^{13}\text{C-NMR}$, FT-IR, GPC, TGA and DSC). Polymeric nanoparticles were formulated in phosphate buffer (pH 7.4) using co-solvent evaporation technique[3]. Characterization of the nanoparticles was performed through $^1\text{H-NMR}$, fluorescence probe technique, AFM, DLS, and ELS methods.

Result and Discussion

Molecular weight distribution and composition of the polymers were determined using GPC and $^1\text{H-NMR}$ spectroscopy, respectively. The splitting of $^1\text{H-NMR}$ resonance at δ 2.3 and δ 4.1 ppm reveals the random copolymerization. Further the presence of the spectral features (FT-IR) corresponding to the PPDO, PCL, and PEG units indicates their presence in the copolymer. In the DSC analysis every polymer showed a single T_g , T_m and T_c . It implies the complete mixing of all the segments of constituent blocks within the copolymers. Polymeric composition was obtained by the qualitative characterization of degradation process illustrated by the inflection point temperature (T_d) and the weight loss percentage (ΔW). TG curve showed two distinct degradation steps. The calculated T_d and ΔW values suggested that the first degradation step was due to the PPDO/PCL and the second was due to the PEG.

Existence of hydrophobic domains as cores of the nanoparticles was characterized by $^1\text{H-NMR}$ spectroscopy (Figure 1). All the characteristic peaks in CDCl_3 (spectrum "A") were in the

agreement with the basic structure of polymer where as the existence of only a signal (h^*) at δ 3.6 ppm in D_2O (spectrum "B") was related to the basic structure of nanoparticles. Critical micelle concentration (CMC) of the polymer in phosphate buffer (pH. 7.4) was decreased from 2.3×10^{-3} to 7.6×10^{-4} g/L with PCL fraction. Atomic force microscopy (AFM) observation showed that the nanoparticles, PPDO-PEG (A), PPDO/PCL-PEG (B), and PCL-PEG (C), were uniform and spherical 50 ~ 30 nm diameter (Figure 2). Dynamic light scattering (DLS) and electrophoretic light scattering (ELS) measurements showed a monodisperse size distribution of around 113 ~ 90 nm hydrodynamic diameters and negative zeta (ζ) potential (-4 to -14 mV), respectively. Thus we found a distinct variation in the physicochemical properties of polymeric nanoparticles with the content of PCL, i.e., T_g and T_c of the polymer. It implies that the micelle yield, drug loading content and entrapment efficiency of PPDO-co-PCL-b-PEO-b-PCL-co-PPDO nanoparticles could be significantly.

Conclusion

The silent feature of the present research was the identification of effect of PCL content on ABA type random triblock copolymers of PPDO-co-PCL-b-PEO-b-PPDO-co-PCL. PPDD-b-PEG-b-PPDO was modified into a semicrystalline and high flexible state by the random insertion of PCL segment. CMC was linearly decreased with increasing the fraction of PCL thereby decreasing particle size. DLS measurement showed that the particle size was less than 120 nm and the hydrophobic segment makes a significant influence on the mean diameter. The investigation for the polymeric nanoparticles into an aqueous medium showed that the composition of the hydrophobic segment makes a significant influence on its physicochemical characteristics. Hence, we believe that these nanoparticles could give a reasonable drug release profile and solubilization effect on the hydrophobic drugs associated with intravenous administration.

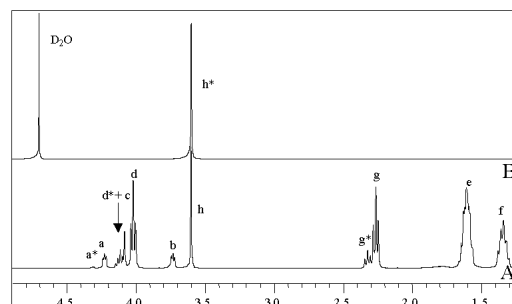


Figure 1

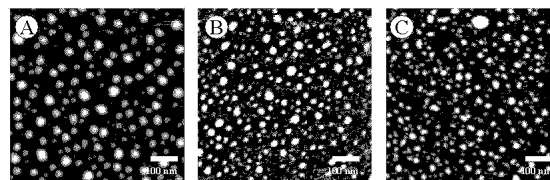


Figure 2

Acknowledgement

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