디옥산원, 락티드 및 폴리에틸렌글리콜로 구성된 트리블럭 공중합체의 수분산 미셀형성계의 특성

나라얀 바타라이, 김 학 용, 딩 빈, 이 덕 래
전북대학교 섬유공학과

Characterization of Water Dispersiable Micelle-Forming System of Triblock Copolymer of PDO, Lactide and PEG

Narayan Bhattarai, Hak Yong Kim, Bin Ding, Duck Rae Lee.
Department of Textile Engineering, Chonbuk National University

1. Introduction

The copolymer of 1,4 dioxan-2-one(PDO) and L-Lactide(LLA); Poly PDO-Co-Lactide is one of the attractive biomaterials for the pharmaceutical and medical application due to it's non toxicity, biocompatibility and biodegradability. Polyether, specially poly(ethylene glycol) has the superior properties of non toxicity , flexibility, hydrophilicity and biocompatibility. A new family of block copolymer can be formed by copolymerization of PDO, Lactide and PEG. The copolymer containing PDO-co-lactide as the hydrophobic block and PEG as hydrophilic block can be dispersed in water to form non ionic micelles. Further more due to the ease of both preparation and incorporation of drug molecules as well as potential for high drug loading and possibilities for sustained systematic release. There is a significant interest in micelles or "self assembling, supermolecular complexes" as microcontainers for drug targeting . For non ionic micelles produced form Poloxamers, which are based of blocks of hydrophilic Poly (oxyethylene) PEO and hydrophibic Poly(oxy propylene) PPO, molecules of drug can be solublized in the inner hydrophobic PPO core, with the PEO blocks forming the outer hydrophilic shell. Similar idea of Poloxamer can be attributed for the water dispersion of the triblock copolymer of PDO, Lactide and PEG.

The present work aims at the synthesis and characterization of amphipathic ABA type block copolymers comprising poly PDO-co-lactide (A) and poly(ehylene glycol) (B), segments; furthermore the characterization and stability of it's water dispersions.

2. Experimental

2.1 Materials.

Poly(ehylene glycol)s (PEGs) with number average molecular weights of 1000, 1500, 2000, 3400, 4000, 10000 (Aldrich) were used after reprecipitation using the methylene chloride solvent and diethyl ether non solvent. 1,4-dioxan-2-one(PDO) and L-Lactide(LLA) were used as synthesized in our laboratory procedure. LLA was used after further recrystallization in ethyl acetate. 1,6-diphenyl-1,3,5 -hexatriene(DPH) was used as received(Aldrich).

2.2 Synthesis of Poly(LLA-co-PDO)-b-(PDO-co-LLA) triblock copolymer

A series of triblock copolymers of PEG blocks with varying molecular weight , PDO and LLA were synthesized. Initially same composition of each monomers by weights were used in each different batches of polymerization. Briefly, appropriate amounts of pure PEG ,LLA and PDO were placed in a flame dried three necked flask and applied for vacuum dry about 12 hours. After purging the nitrogen on it, stannous octoate catalyst(0.01%w/w) was added as a solution in toluene. The reactants were further dried under vacuum at 60℃ till the effervescence of toluene was stopped. The co polymerization was carried out at 160℃ for 20 hours. under nitrogen and stirring condition. The product was dissolved in dichloromethane and precipitated into an excess of diethyl ether. The purified copolymers were dried in vacuum oven at 80℃ till the constant weight was obtained.

The series of triblblock copolymers were analyzed by ^1H NMR Spectroscopy using $CDCl_3$ as the solvent, Gel Permeation Chromatography(GPC), IR, DSC and Inherent vescosity.

2.3 Preparation of Water Dispersion

The copolymers were dissolved in methylene chloride and then dropped into the aqueous phase(de ionized water). The resulting solution was stirred constantly and methylene chloride was evaporated out over night. All dispersions were filtered through disposable 1 μm filters.

2.4 Evaluation of Dispersion Stability.

The dispersion stability to added electrolyte was studied by adding 0.5 *ml* of each dispersion to 2.5 *ml* of Na_2SO_4 solution of varying concentration(0-0.8 *M*) and measuring the absorbance of turbidity at a wave length of 300 *nm* after 15 *minutes*(UV-VIS Spectrophotometer).

2.5 Micelle Characterization

The micellization was studied using the dye solublization and ^{13}C-NMR Spectra methods. DPH solution (50 μl of 0.4 *mM*) in methanol was injected using micro syringe into 5 *ml* triblock copolymer solution and left for 12 *hrs* in room temperature before UV measurement. ^{13}C-NMR spectrums were obtained in CDC_{13} and D_2O solvent.

3.Result and Discussion.

3.1 Characterization of triblock copolymer.

The formation of triblock co polymer were confirmed by the appearance of characteristic peaks in ^1H NMR, ^{13}C NMR and IR. The increasing order of dilute solution viscosity of each copolymers(0.1 *dl/g* in HFIP solvent at 25℃) in accordance with increasing order of initial PEG molecular weight contained, showed the molecular weight of final purified triblock copolymer increased with the increase of PEG molecular weights which could be further confirmed from the GPC(Fig. 1) and DSC thermograms(Fig. 2).

3.2 Stability and Micellization

Triblock copolymers of lower molecular weights were clearly soluble in water below room temperature where as the high molecular weights were in milky white dispersions. The clear solution of the copolymers were clouded at different temperatures depending on it's aqueous solution concentration.

Since the copolymer contains the hydrophobic and hydrophilic blocks, it has the tendency to form micelles in water to reduce free energy mainly from hydrophobic interactions. The absence of characteristic NMR peaks of hydrophobic blocks of the triblock copolymer using D_2O solvent in ^{13}C NMR spectrum confirmed the formation of micelles of triblock copolymers, which was not happened in CDC_{13} solvent because CDC_{13} was non selective solvent for both hydrophilic and hydrophobic part(Fig. 3). This fact was also confirmed by the hydrophobic dye solubilization method. The hydrophobic dyes were preferentially partitioned into the hydrophobic part of micelles, resulting the increase in the absorbance of the dye(Fig. 4).The concentration at which solublization of springly soluble solute increased in the presence of a surfactant was conventionally taken as the critical micelle concentration(CMC) which could be obtained at the cross point of extrapolating of the absorbance at low and high concentration regions(Fig. 5).

The increase in turbidity of the polymer solution with the increase of Na_2SO_4 solution concentration was due to the SO_4^- anions which were thought to be unhydrated in aqueous solution and reduced the solvency power of the medium for

the PEG(Fig.6).

4. Conclusion

The triblock copolymer of PDO, LLA and PEG was possible for formation of micelles like dispersions. Micelle core (hydrophobic part) of the triblock copolemer could be served as the cargo space for the various lipophilic drugs in the sustained release process.

5. References

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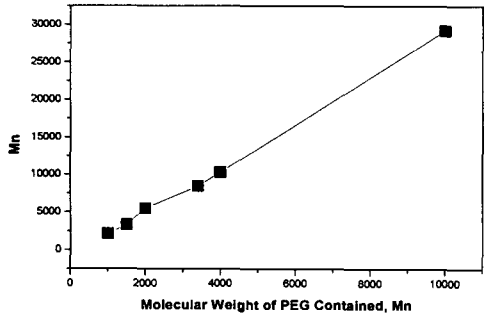


Fig. 1. Effects of PEG molecular weight on Mn of triblock copolymer.

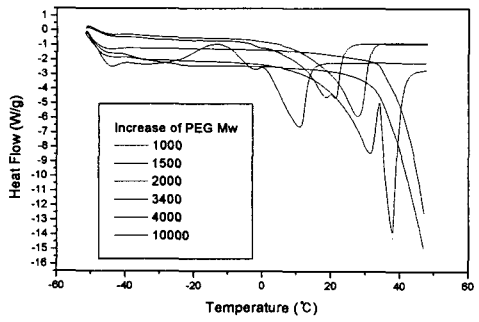


Fig. 2. DSC thermograms of triblock copolymers at some different PEG molecular weights(Numbers indicate Mn of PEG).

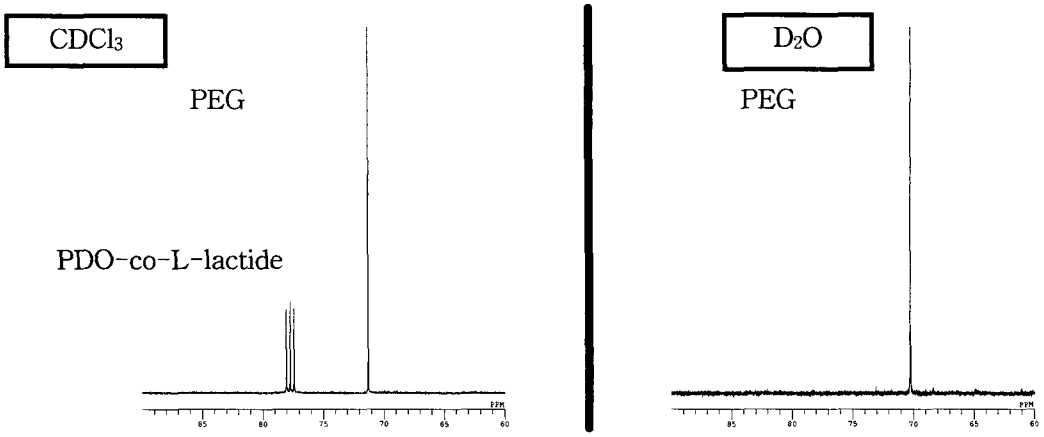


Fig. 3. Comparison of ^{13}C-NMR spectra of triblock copolymer of PDO, L-lactide and PEG in $CDCl_3$, D_2O.

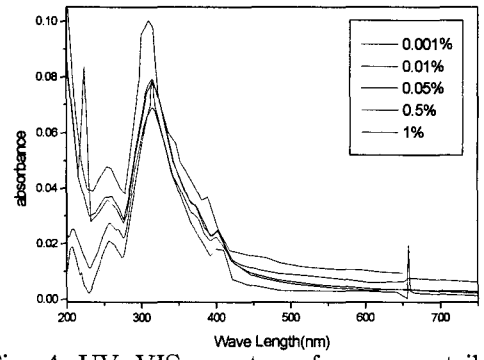


Fig. 4. UV-VIS spectra of aqueous triblock copolymer (Mn:8444) solutions containing hydrophobic dye(DPH) at 20℃. (Polymer conc.; 0.001, 0.01, 0.05, 0.5, 1 wt%, while dye conc.; 4 mM).

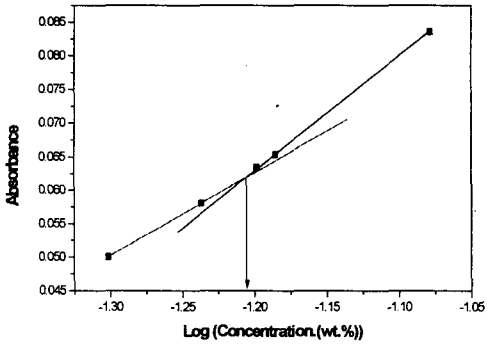
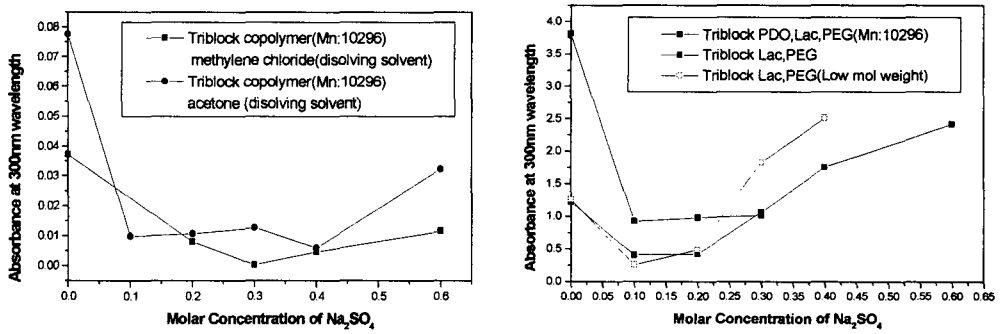


Fig. 5. Determination of CMC by extrapolation method.



A B

Fig. 6. Comparison study for the stability of Aq. triblock copolymer dispersions by turbidity method(A: same copolymer, B: different copolymers).