Korea Polymer Journal, Vol. 6, No. 3, pp 249-255 (1998)

Preparation and Characterization of the Biodegradable Microgels Based on Poly(caprolactone diol)

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Received March 12, 1998

Abstract : This paper describes the formation of microgels from poly(caprolactone diol) with the molecular weight of 2125(PCD-2125), 3,4-dihydro-2H-pyranyl-2-methyl(3,4-dihydro-2H-pyran-2-carboxylate), and crosslinking agent, 1,2,6-hexanetriol by solution polymerization in various solvents. A critical gelation concentration in various solvents, the molar ratio of monomers, the solubility parameter of the solvents and the monomer concentration were found to be the important factors influencing the formation of microgels or macrogels. The microgels based on PCD-2125 were semicrystalline solid powder with the crystalline melting endotherm at around 49.6~52.1 ℃. It was found that the microgels are small particles below 100 nm and critically packed at the concentration of 11~12 g/100 mL below the critical gelation concentration.

Introduction

The microgels are the crosslinked polymer particles with three dimensional structure and fixed surfaces but are still soluble in certain solvents like most of the linear or branched polymers. Most of microgels had been usually synthesized by emulsion or soap free radical polymerization.[1-12] The particle size distribution and molecular weight of polymer microgels are different according to polymerization method, but only obtained polymer particles which have particle size in the range of micro size in diameter. A general hypothesis by which microgels would be expected to be formed from polyfunctional monomers in good solvents, and at complete conversion to polymer but without macrogelation, has been previously proposed and demonstrated for radical addition polymerization.

N.B. Graham[13] presented the practical demonstration of this hypothesis by experimental extension to step-growth polymerization. In the study on microgel preparation by solution polymerization of monomers with di- or tri-functionality, Graham and Mao[14-16] showed that the microparticulate stage of the reaction could be prolonged to allow the molecular weight to increase while retaining the small particle of nanosize, and also discussed the mechanism of the microgel formation.

Studies on preparation and charaterization of the microgels have become more and more attractive because of the special and interesting characters of microgels such as various size, large surface area, various swelling degree and others. There has been increasing interest for use in biomedical application such as drug delivery system.[17-19] Poly(caprolactone) is known as a family of biodegradable aliphatic polyesters which have found importance as biomedical applications due to its biocompatibility and bioabsorbability.[20]

In this study, microgels were prepared from poly(caprolactone diol) in stoichiometric combination with various molar ratio of 3,4-dihydro-2H-pyranyl-2-methyl-(3,4-dihydro-2H-pyran-2-carboxylate) and 1,2,6-hexanetriol as the crosslink-

ing agent by solution polymerization. We studied on the relationship between gelation concentration and solubility parameter of the solvents, and critical gelation concentration for various molar ratio of monomers. The objective of this study is to study effects of monomer concentration on the microgel formation. We also investigated the physical properties of the microgels such as intrinsic viscosity, coil density, molecular weight, and thermal properties of the microgels.

Experimental

Materials. Poly(caprolactone diol) (PCD) and 1,2,6-hexanetriol (HT) were obtained from Aldrich Chem. Co. and the number average molecular weight of the PCD was determined by using the hydroxyl number analysis method (ASTM D 1638 67T). The number average molecular weight of the PCD is 2125(PCD-2125). PCD was vacuum dried on Rotavapor at 90~95 °C for at least 6 hrs., and was stored molten in an oven at 80 °C until use.

HT was used as the crosslinking agent and it was vacuum dried following the same procedure as drying PCD. 3,4-Dihydro-2H-pyranyl-2-methyl-(3,4-dihydro-2H-pyran-2-carboxylate) (C1) was obtained from Polysystems Ltd., and distilled around 110~115 °C under a pressure of 0.1 mmHg.

Organic solvents such as acetone, methyl ethyl ketone (MEK), 3-pentanone, 2-hexanone, cyclopentanone, cyclohexanone and ethyl carbonate used for the reactions were dried over anhydrous calcium sulfate (20-40 mesh) and molecular sieve (4A type, 20 mesh) followed by distillation. Anhydrous ferric chloride was supplied by BDH and used directly as a catalyst for the microgel preparation. Petroleum ether(bp. 60~80 °C) and methyl alcohol were used as solvents to precipitate microgels from reaction solution.

Preparation of the Microgels. Microgels were prepared by the solution polymerization of PCD, HT and C1. The amounts of the reactants were measured precisely so as to give stoichiometric compositions of two hydroxyls for each double bond of C1. The molar ratios of the monomers were PCD/HT/C1: 1/1/2.5, 1/1.5/3.25, 1/2/4.0, 1/3/5.5, 1/4/7.0. Table I lists the formulations for microgel preparation used in this study.

A typical example of the microgel preparation is as follows; Given amount of PCD, HT and C1 were mixed in a capped Wheaton serum bottle, and was dissolved in weighed amount of solvent at 60 °C. The appropriate volume of 5%(w/v) solution of anhydrous $FeCl_3$ was added. And then the weight of reaction mixture was finally adjusted by the addition of a solvent to provide the desired concentration of the total reactants. The bottle was then sealed and placed in an oven at 60~80 °C for 24 hrs. The reaction was carried out in the concentrations ranging from 10 to 70% at an interval of 5 or 10%(w/w) monomer concentration. Microgels were collected from their reaction solution by precipitation using excess petroleum ether in an ice bath. The precipitate was suspended in methanol and left in a freezer overnight. The microgels was filtered, washed with methanol, and dried at room temperature under vacuum for a week.

Table I. The Composition of PCD, HT and C1 for the Preparation of Microgels

Sample Code	Molar Ratio (PCD/HT/C1)	HT (mole %)	Weight of Reactants (g)			Reactant Conc. (% w/w)
			PCD	HT	C1	
$P_1H_1C_{2.5}$	1/1/2.5	22.1	2.50	0.61	2.55	5.66
$P_1H_{1.5}C_{3.25}$	1/1.5/3.25	26.1	2.50	0.91	3.31	6.72
$P_1H_2C_{4.0}$	1/2/4.0	28.6	2.50	1.22	4.07	7.79
$P_1H_3C_{5.5}$	1/3/5.5	31.6	2.50	1.83	5.60	9.93
$P_1H_4C_{7.0}$	1/4/7.0	33.3	2.50	2.44	7.13	12.07

* Microgels were prepared at an interval of 2.5 grams PCD.
PCD : Poly(carprolactone diol).
HT : 1,2,6-Hexanetriol.
C1 : 3,4-Dihydro-2H-pyranyl-2-methyl(3,4-dihydropyran-2-carboxylate).

Characterization of the Microgels. Infrared spectra were obtained using IR spectrophotometer(JAS. Co. Report-100) and molecular weights were determined by gel permeation chromatography (GPC, Waters M 510). The equip- ment consisted of stragel column (HR 4+ HR 2+HR 0.5) with normal pore size of 10^2~10^6 nm. The sample solution in THF was eluted at a flow rate of 1.0 mL/min. The μ-stragel columns were calibrated polystyrene standard. The viscosities of the microgel dissolved in $CHCl_3$ were carried out using an Ubbelohde viscometer at 25 ℃.

Differential scanning calorimetry (DSC, Dupont 9900) was carried out using thermal analyzer with a differential scanning calorimeter cell under N_2 atmosphere with a heating rate of 10 ℃/min. The sample was 10~12 mg and the temperature range was -100 to 150 ℃.

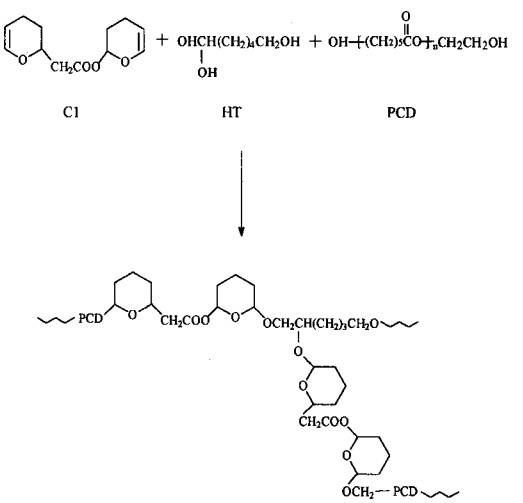
Optical microscopy (Dong Won, EML-TS) of the microgels was carried out under polarized light. Specimens were prepared by placing the recovered microgels on around cover glass. Morphology and shape of the microgels were observed on a scanning electron microscope (SEM, Joel JSM-840A). The microgels were mounted and sputter coated with gold using a sputter coater. The microgel was dissolved in acetone and the solution was dropped and dried on a copper grid coated with a carbon substrate. Particle size measurement were performed on transmission electron microscopy (TEM, Zeiss EM 109).

Results and Discussion

In order to investigate the reaction conditions for microgel preparation based on poly(caprolactone diol) (PCD-2125), the relationship of gelation concentration and solubility parameter of the solvents, and critical gelation concentrations for various molar ratios, PCD/HT/C1 of 1/1/2.5($P_1H_1C_{2.5}$), 1/1.5/3.23($P_1H_{1.5}C_{3.25}$), 1/2/4.0($P_1H_2C_{4.0}$), 1/3/5.5($P_1H_3C_{5.5}$) and 1/4/7.0($P_1H_4C_{7.0}$) were carried out, respectively.

The C1 quantity was used the stoichiometric amount for complete reaction of the hydroxyl group of PCD and HT. The schematic structure of the microgels was shown in Scheme I.

The complete reaction between hydroxyl groups



Scheme I. The schematic structure of the microgel based on poly(caprolactone diol).

and double bond was indicated by the disappearance of the IR peak at 1648~1654 cm^{-1} which is assigned to the double bonds of C1. The expected formation of ether linkage was indicated by the disappearance of the IR peak at 3400~3500 cm^{-1} which is assigned to be the hydroxyl groups of PCD and HT.

The relationship between microgelation concentration of $P_1H_1C_{2.5}$ and the solubility parameter of the solvents is shown in Figure 1.

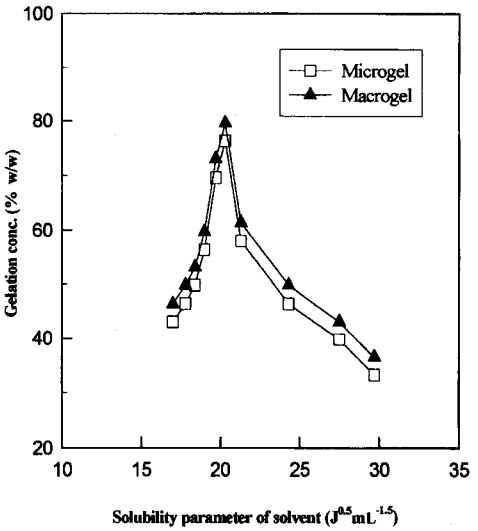


Figure 1. The relationship between gelation concentration and the solubility parameters of the solvents.

The solubility parameter of solvents used for the reactions are following : 2-hexanone(17.0 $J^{0.5}mL^{-1.5}$), 3-pentanone (17.8 $J^{0.5}mL^{-1.5}$), MEK-3-pentanone (50/50 v/v, 18.4 $J^{0.5}mL^{-1.5}$), MEK (19.0 $J^{0.5}mL^{-1.5}$), acetone-MEK (50/50 v/v, 19.7 $J^{0.5}mL^{-1.5}$), cyclohexanone (20.3 $J^{0.5}mL^{-1.5}$), cyclopentanone (21.3 $J^{0.5}mL^{-1.5}$), EC-MEK(40/60 v/v, 24.3 $J^{0.5}mL^{-1.5}$), EC-MEK(80/20 v/v, 27.5 $J^{0.5}mL^{-1.5}$) and EC (29.7 $J^{0.5}mL^{-1.5}$). For each solvent used, there was a critical concentration of the monomer for the microgel formation. Also the macrogel formation was observed above the maximum microgelation concentration. Stable microgel solutions were obtained when the monomer concentration was below the critical gelation concentration. The maximum critical gelation concentration was observed at around of 20.3 $J^{0.5}cm^{-1.5}$.

In solvent of low solubility parameter such as 2-hexanone, the microgel was formed at very low monomer concentration. Even in solvent of higher solubility parameter such as EC and EC-MEK (80/20 v/v), the gelation also led to heterogeneous mixtures of the gel which could not be dissolved in solvents. It was also observed that the monomer gelation concentrations are different in various solvents of the different solubility parameter. This could be due to the change in the solubility parameter for PCD, and the change in the crosslinked density by the packing effect of the chain length of PCD. In this reaction, PCD would probably act as a good stabilizer, preventing the microgel particles from intermolecular reaction. It could be explained by auto-steric stabilization mechanism for the formation of the microgels which was suggested by Graham and coworkers.[15,16]

The critical microgelation concentration against molar % of HT is shown in Figure 2. We could select the good solvent for the microgel preparation from the relationship between critical microgelation concentration and molar % of HT in various solvents. MEK, acetone-MEK and cyclohexanone are good when PCD chains are acting as the steric stabilizer. The critical gelation concentration for molar ratios of monomer in cyclohexanone was comparatively higher. However, it was not easy to take precipitate out completely from viscous fluid of the reaction solution. It is

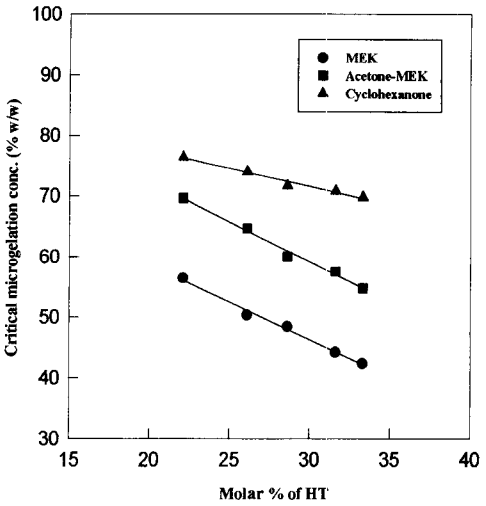


Figure 2. The critical microgelation concentration as a function of molar % of HT in various solvents.

shown that critical microgelation concentration for the microgel formation decrease with increasing molar % of HT. In this study, we decided to select the mixed solvent of acetone-MEK for the preparation of microgels.

Molecular weight (M_n and M_w) of the microgels from GPC measurements are presented in Figure 3. Against the reactant concentration molecular weight decreased below the reactant concentration of 20%(w/w) and then increased sharply up

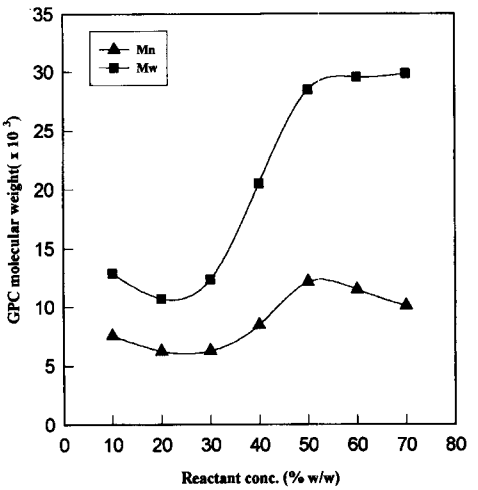


Figure 3. The molecular weight of the microgels for $P_1H_1C_{2.5}$ against reactant concentration where reaction proceeded at 80 °C for 24 hrs.

to 50%(w/w). This probably represents that the chain extension resulted from the reaction of PCD with C1 initially, and then the formed linear polymers transform to crosslinked polymers. We could explain that the decreasing of the molecular weight was again due to transform from linear or branched structure to a crosslinked structure. Otherwise, number average molecular weight (M_n) of the microgels was decreased over the reactant concentration of 50%(w/w). These GPC molecular weights are due to measure plotted hydrodynamic volumes rather than a absolute molecular weight by GPC technique. The polydispersity of the microgels were in the range of 1.71~2.78.

Intrinsic viscosities of the microgels in $CHCl_3$ at 25 ℃ were measured and coil densities were calculated from the intrinsic viscosities using the Einstein equation, $[\eta]=2.5/\rho c$, where, $[\eta]$ is the intrinsic viscosity in g/100 mL. The coil densities of the microgels are shown in Figure 4. The microgels were prepared over all reactant concentration of 11~12 g/100 mL.

It is shown that most of the microgels have been prepared at concentration above critical packing. This indicates that steric stabilization is very efficient and prevents interparticle reaction below critical gelation concentration. Typical DSC thermogram of the microgels is shown in Figure 5. Glass transition temperature(T_g) of the microgels could be seen in the region of -10.3~-38.6 ℃. Its crystalline melting temperature(T_m) indicated the sharp crystalline melting endotherm between 49.6~52.1 ℃.

As shown in the DSC curve of the microgel film, the exothermic peak preceding the melting exotherm is due to the cold crystallization.[21] Crystallinity of the microgels was calculated assuming proportionality to the experimental heat of fusion utilizing the reported enthalpy of fusion of 139.5 J/g for 100% crystalline poly (caprolactone).[22] T_g and T_m show the dependence of molar % of HT. The crystallinity decreased with increasing the crosslinked density as we expected.

From the optical micrographs shown in Figure 6 fine-grain texture of polygonal spherulite could

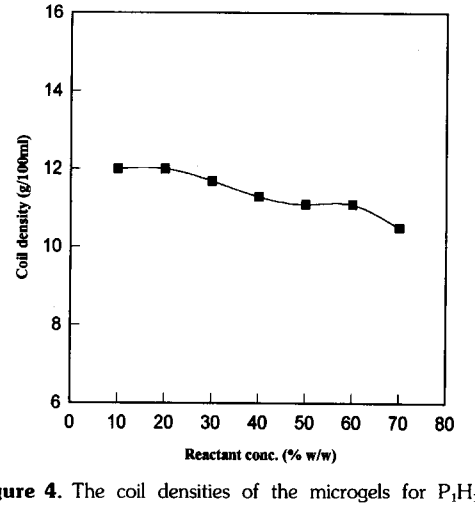


Figure 4. The coil densities of the microgels for $P_1H_1C_{2.5}$ from the intrinsic viscosities in chloroform at 25 ℃.

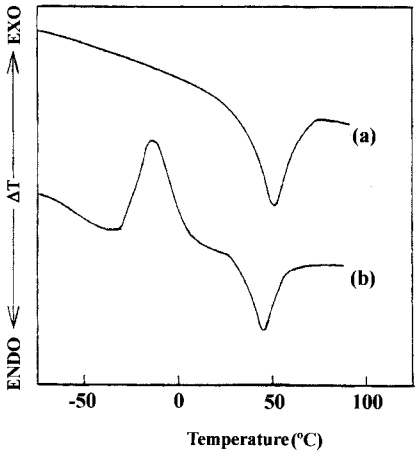


Figure 5. Typical DSC curves of the microgel (a) powder and (b) casting film for $P_1H_1C_{2.5}$.

Figure 6. The optical photographs of the microgel film for $P_1H_1C_{2.5}$ under polarized light observed at (a) room temp., (b) crystallization and (c) melting temp.

Table II. The Physical Properties of the Microgels Obtained at Critical Microgelation Concentration

Sample Code	Reactant Conc. (% w/w)	T_g (°C)	T_m (°C)	ΔH(J/g)	Crystallinity[a]	Coil Density[b]	M_w[c]
$P_1H_1C_{2.5}$	70	-10.3	52.1	68.2	48.8	10.5	22,000
$P_1H_2C_{4.0}$	60	-17.6	51.2	57.4	41.2	10.9	28,000
$P_1H_4C_{7.0}$	50	-38.6	49.6	45.2	32.4	12.8	34,000

[a] Crystallinity was calculated from the fusion of 139.5 J/g for 100% crystalline state.
[b] Coil density was calculated from intrinsic viscosity using the Einstein equation, $[\eta]=2.5/\rho c$.
[c] Molecular weight was determined by light scattering spectroscopy.

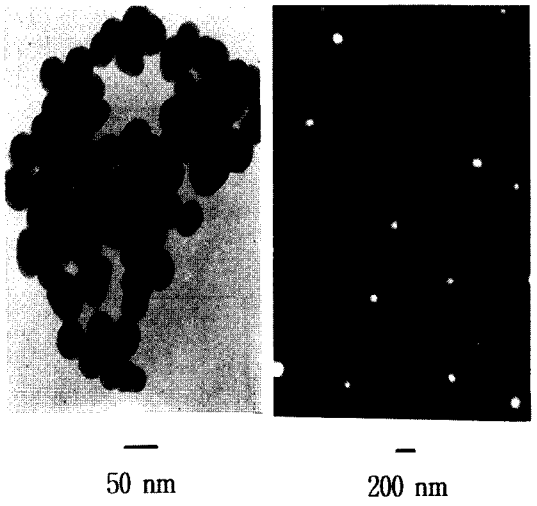


Figure 7. A transmission electron micrograph (a) and a scanning electron micrograph (b) of $P_1H_1C_{2.5}$ microgel.

be seen at room temperature. Otherwise, it could be seen that the shearlike lamellae structure was formed by crystallization on cooling of their melts while the micro- and macro- domains were formed by phase separation at crystalline melting temperature. Electron micrographs in Figure 7 very clearly showed the phase separation of the microgels. Small particles below 100 nm are distributed and uniformly spherical in shape, but are slightly aggregated shape. Physical properties of the microgels obtained at around critical gelation concentration were summarized in Table II.

T_g, T_m and crystallinity of the microgels were decreased with increasing the crosslinked degree. The coil density of the microgels was overall reactant concentration 11~12 g/100 mL, and weight average molecular weight was distributed in the region of $2.2\sim3.4\times10^4$.

Conclusion

The microgels were prepared from poly (caprolactone diol) (PCD-2125) in stoichiometric combination with various molar ratio of C1 and HT by solution polymerization. In the preparation of microgels, the relationship between gelation concentration and solubility parameter of the solvent, and between critical gelation concentration and various molar ratio of PCD/HT/C1 were investigated.

For each solvent used, there was a critical gelation concentration of monomers for the microgel formation. The maximum critical gelation was observed at around of 20.3 $J^{0.5}mL^{-1.5}$. The effect of monomer concentration on the microgel formation was investigated by the GPC measurement. The coil density of microgels was calculated from the value of intrinsic viscosity using Einstein equation. It was found that the microgels prepared over all reactant concentration of 11~12 g/100 mL. Glass transition temperature of the microgels could be seen in the region of -10.3~-38.6 °C. Its crystalline melting temperature indicated the sharp crystalline melting endotherm between 49.6~52.1 °C. It has been observed that these are uniformly spherical but slightly aggregated network particles below 100 nm.

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