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MULTICOMPONENT POLYMERS OF POLY(LACTIC ACID) MACROMONOMERS WITH METHACRYLATE TERMINAL AND COPOLYMERS OF POLY(2-HYDROXYETHYL METHACRYLATE)

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ABSTRACT

Poly(lactic acid) macromonomers with methacrylate terminal functionality have been synthesized from the cyclic dimer of lactic acid (referred to as lactide) with 2-hydroxyethyl methacrylate (HEMA) as initiator and stannous 2-ethyl hexanoate as catalyst. The macromonomers were characterized with FT-IR, NMR, GPC, DSC, WAXS, and CD. The molecular weights of the macromonomers ranging from M_n 1425 to 19,169 are predictable from the lactide/HEMA ratio in the polymerization feeds. The properties of the macromonomers vary with the stereochemistry of the lactide and the composition. Circular dichroism measurements demonstrate that there is little racemization during polymerization.

INTRODUCTION

Homo- and copolymers of lactic acid (PLA) have received increasing interest as biodegradable polymers [1–5]. However, there are limitations of the currently available linear PLAs. Among these are the complicated mechanisms of degradation of partially crystalline poly(L-lactic acid) (PLLA) copolymers [4], the difficulty in processing, and the physical aging of processed PLLA [6]. In certain applications the balance of hydrophilicity and hydrophobicity is preferred over the highly hydro-

phobic polyesters. The presence of methyl substituents in PLA limits its compatibility with soft tissues due to the reduced hydrophilicity.

We demonstrated that multicomponent systems containing hydrophobic polycaprolactone (PCL) and poly(2-hydroxyethyl methacrylate) (PHEMA) are advantageous [7–10]. The presence of partially crystalline PCL greatly improves the strength of PHEMA hydrogels. Since PLLA has a much higher T_g and T_m than PCL, the PLA–PHEMA combination should provide hydrophilic–hydrophobic materials of higher useful temperature than PCL–PHEMA systems. Among our approaches to combine hydrophilic and hydrophobic polymer systems is the use of macromonomers. We reported [11, 12] the synthesis and polymerization of methacrylate-terminated poly(lactic acid) macromonomers using 2-hydroxyethyl methacrylate as initiator with stannous 2-ethyl hexanoate as catalyst. More recently similar macromonomer preparations with aluminum alkoxide as initiator were reported by other groups [13, 14]. We report here our continuing work on these macromonomers.

EXPERIMENTAL

Materials

Stannous 2-ethyl hexanoate and 2-hydroxyethyl methacrylate (HEMA) were purchased from Sigma Chemicals. The (3*S*)-*cis*-3,6-dimethyl-1,4-dioxane-2,5-dione (L-lactide) and 3,6-dimethyl-1,4-dioxane-2,5-dione-2,5-dione (D,L-lactide) were obtained from Sigma Chemicals. The lactide monomers were purified by recrystallization from toluene and oven dried in vacuo prior to use.

Synthesis of Methacrylate-Terminated PLA Macromonomers

The bulk polymerization reactions were performed in reaction vessels equipped with magnetic stir bars and nitrogen gas inlets. The lactide, HEMA, and stannous 2-ethyl hexanoate were charged into the reaction vessels to obtain the various copolymer compositions (0 to 10 mol% HEMA) and polymerized at 110–120°C in a silicone oil bath for 24 hours. For comparison, a poly(D,L-lactide-HEMA) series containing 0 to 10 mol% HEMA was prepared starting from D,L-lactide. Further, polymerization of L-/D,L-lactide and HEMA was carried out to obtain copolymers of different stereochemical compositions (0 to 40 mol% D,L). After polymerization was complete, the products were dissolved in chloroform, precipitated into cold methanol, and dried at 80°C in vacuo for 24 hours.

Poly(lactide-HEMA) macromonomer. Typical yield(s): 82–98%. Elemental analysis of poly(LLA-HEMA) containing 10 mol% HEMA: Calculated, C 49.5, H 5.65, and O 44.8%; found, C 50.4, H 5.67, and O 43.8%. FT-IR (cm^{-1}): 3518 (OH end groups), 2950 (CH stretch), 1753 (C=O ester), 1639 (C=C stretch).

Copolymerization of HEMA with Methacrylate-Terminated PLA Macromonomers

The poly(LLA-HEMA) macromonomers were used to prepare graft copolymers of various compositions via free-radical copolymerization with HEMA monomer. Azobis(isobutyronitrile) (AIBN) free-radical initiator was used at concentra-

tions of 0.1 to 1% (w/w). The grafting reaction was performed at 70°C for 24 hours.

Characterization

NMR measurements (270 MHz) were recorded using a Bruker NMR instrument model AC-270. Thermal properties of the macromonomers were investigated using a Perkin-Elmer DSC 7 instrument at a heating rate of 20°C (−50 to 200°C). Wide-angle x-ray scattering (WAXS) powder patterns were obtained using a Norelco diffractometer. The diffraction patterns were collected at a power setting of 30 kV and 15 mA and 500 counts/s. The molecular weight determinations were done using a Waters gel permeation chromatograph (GPC) model 510. Elemental analysis was performed at Galbraith Laboratories. The optical activity measurements of the copolymers were determined at 24°C using a polarimeter. Circular dichroism (CD) spectra of the polymers in $CHCL_3$ were measured in 1 cm path length cuvettes at 25°C using a Jasco J-710 CD spectrometer.

RESULTS AND DISCUSSION

Polymer Synthesis

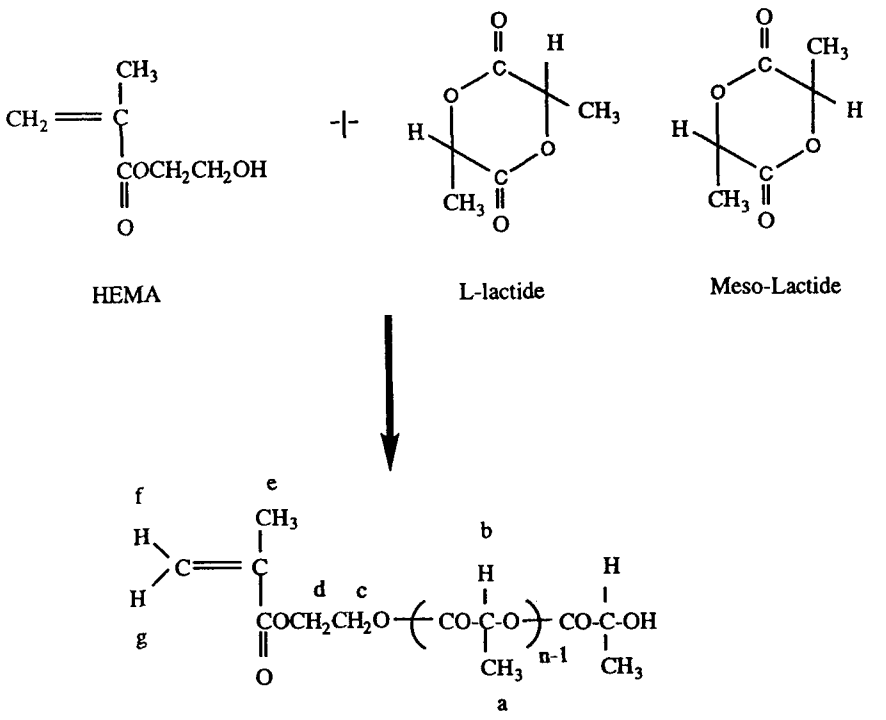
In order to fulfill the requirements for biodegradability a series of copolymers of various stereo chemical composition derived from L-/D,L-lactide and HEMA were synthesized. An outline of the synthesis of poly(lactide–HEMA) copolymers is shown in Scheme 1. Bulk polymerization of the comonomers afforded the corresponding copolymers in good yields (82 to 98%). Elemental analysis performed on the poly(LLA–HEMA) copolymers demonstrate good agreement between the theoretical and experimental values. Verification of the formation of the copolymers was done by FT-IR analysis, confirming the presence of C=C stretch at about 1639 cm^{-1} corresponding to HEMA moiety. Both ^1H- and ^{13}C-NMR analysis were performed to confirm that HEMA was incorporated into the copolymer. The spectra presented in Fig. 1, and the ^{13}C-NMR data are consistent with the expected structure of the copolymers. The striking feature is the downfield ^{13}C chemical shift values of olefinic HEMA carbon types 1 and 2 (δ 126 and 136 ppm) analogous to the downfield ^1H-NMR absorption's of proton types f and g.

Polymer Properties

Methacrylate-Terminated PLLA Macromonomers

The end use properties of polymers generally show great dependency on their glass transition and melting temperatures (T_g and T_m) and degree of crystallinity. All the poly(LLA–HEMA) macromonomers investigated exhibited both amorphous and crystalline behavior as shown in Table 1. In the case of PLLA reference material (Boehringer), T_g and T_m values of 62.2 and 181°C, respectively, were obtained.

The PLLA homopolymer prepared in our study showed T_g and T_m values of 60.8 and 175°C, respectively. However, with the incorporation of HEMA both the glass transition and melting temperatures showed a gradual decrease. Figures 2 and



SCHEME 1. Synthesis of poly(lactide-HEMA) copolymers.

3 illustrate the decreasing T_g and T_m profiles obtained, respectively, as the HEMA content is increased from 0 to 10 mol%.

Table 2 summarizes the crystallinity values obtained using DSC measurements. The crystallinity of the copolymers were evaluated using the equation

$$X_c(\text{polymer}) = \Delta H^*/\Delta H_{PLLA}$$

whereby ΔH^* is the apparent heat of fusion (J/g) of the copolymers. ΔH_{PLLA} refers to the enthalpy of fusion of PLLA (78.6 J/g) calculated from DSC and x-ray data [15]. As shown in Table 2, the crystallinity values obtained for PLLA vary from 47.6 to 59.8% compared to literature values of 57 [5] and 73% [16] annealed at different temperatures.

The similar diffraction patterns obtained for PLLA and P(LLA-HEMA) copolymers demonstrate that incorporation of HEMA does not significantly affect the crystalline packing of the materials. In the case of PHEMA homopolymer, the broad WAXS diffraction peak is indicative of an amorphous polymer (Fig. 4).

Poly(D,L-Lactide-HEMA) Copolymers

The thermal behavior of P(DLLA-HEMA) copolymers were also evaluated using DSC. The data presented in Table 3 indicate that all the copolymers formed

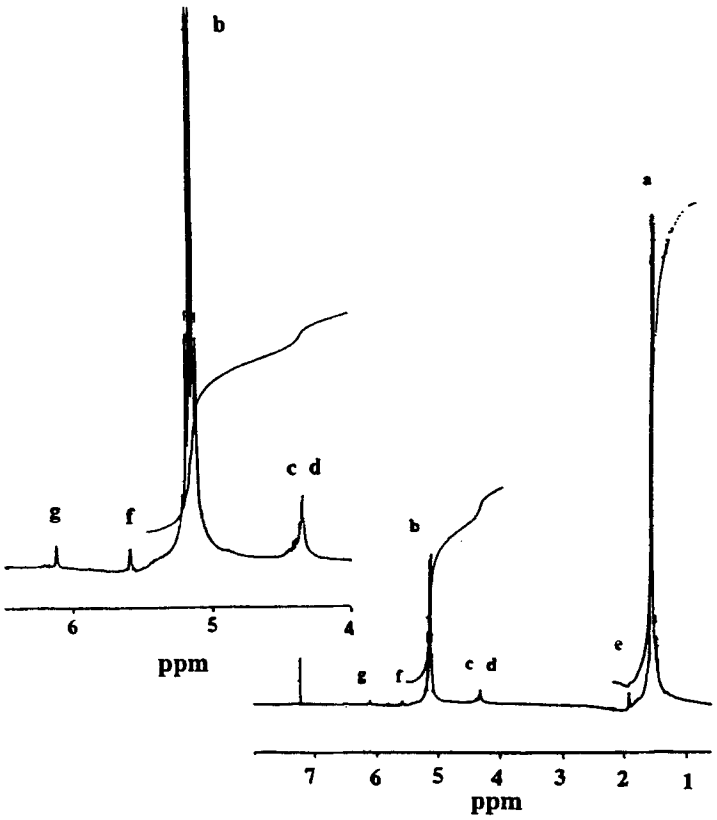


FIG. 1. Typical NMR spectra of P(LLA-HEMA) macromonomer (10 mol% HEMA).

are amorphous materials characterized by T_g values slightly lower than the corresponding P(LLA-HEMA) series.

Variation of Stereochemical Composition

Table 4 shows that the stereochemistry of the P(LA-HEMA) macromonomers can be controlled by varying the mol% L-/D,L-lactide content. The data suggest that incorporation of 10 mol% D,L-units results in a decrease of the melting temperature from 142 to 112°C (10 mol% HEMA content). In a related study of PLLA stereochemistry effects, a critical disruption of the crystalline order caused by the introduction of 8 mol% D repeat units was reported [5]. The results of our study demonstrate that the high crystallinity of the P(LLA-HEMA) copolymers can be modified to a desired level, and this approach provides a means of regulating polymer degradation. It is interesting to note that whereas addition of 10 to 40 mol% D,L-units drastically affects the T_m values, the T_g of the copolymers (10 mol% HEMA) essentially remains the same.

TABLE 1. Thermal Properties (II Scan)[a] of Poly(L-Lactide-HEMA)

Polymer % HEMA	T_g	T_m	ΔH_m	T_c	ΔH_c
PLLA[b]	62.2	181	47.0	106	−29.8
PLLA-12[c]	58.3	175[d]	46.3	—	—
	58.1	171	37.4	126	−21.4
1	50.9	167	47.6	98.4	−20
2	47.8	163	46.0	91.4	−34.1
4	46.9	155	55.6	87.1	−33.6
6	41.5	151	50.2	78.6	−32.7
8	40.7	149	48.4	86.3	−34.8
10	35.7	142	43.6	79.8	−32.8

[a]Temperature in °C and enthalpy in J/g.
[b]Polylactide (Boehringer).
[c]Poly(L-Lactide) LLA/stannous octoate mol ratio = 133.
[d]I scan.

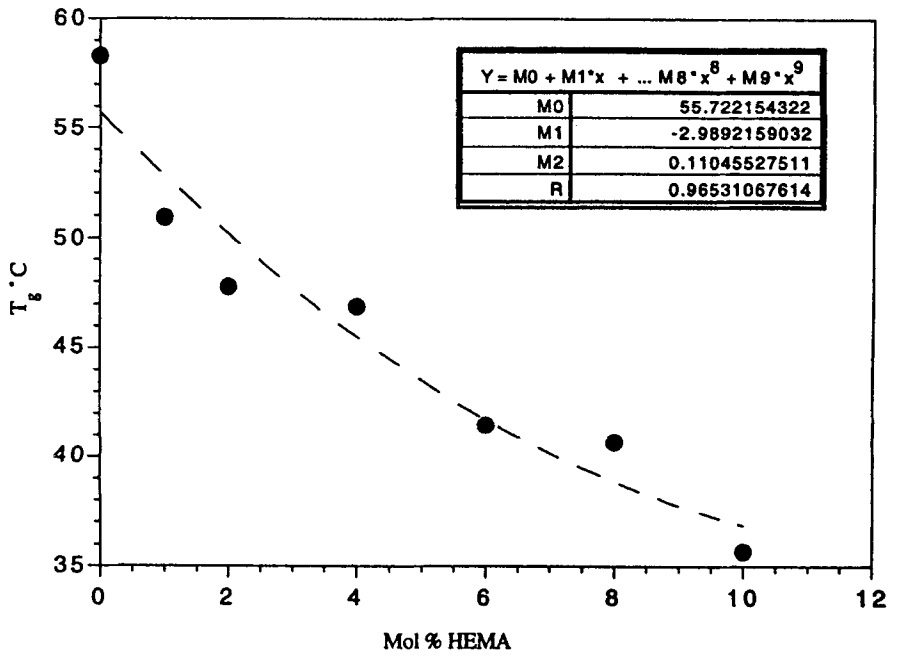


FIG. 2. Effect of composition on T_g of P(LLA-HEMA) copolymers.

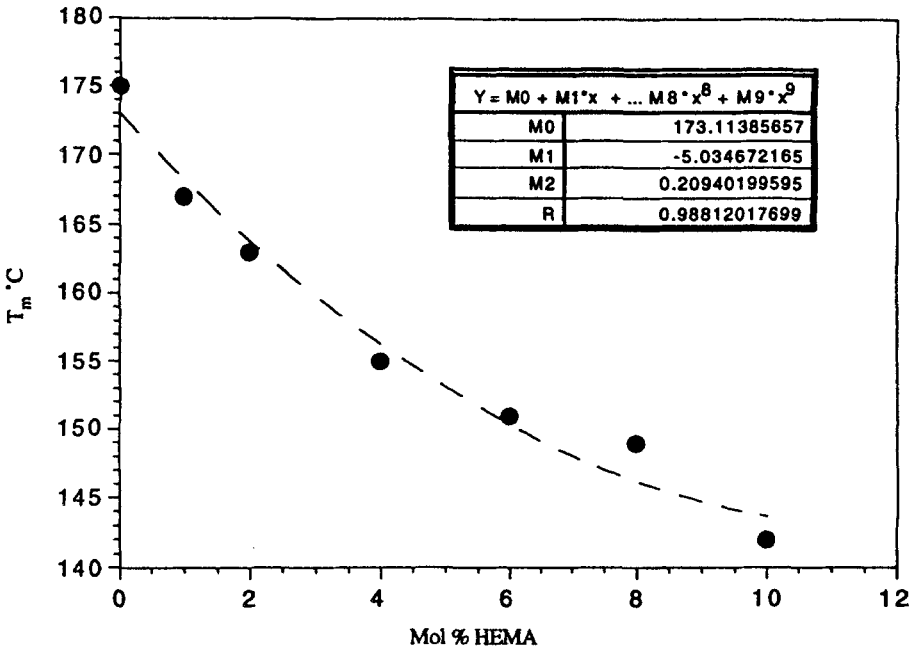


FIG. 3. Effect of composition on T_m of P(LLA-HEMA) copolymers.

Molecular Weights and Molecular Weight Distributions

The results presented in Table 5 show close agreement between the molecular weights determined using GPC and theoretical values. The molecular weight distribution (M_w/M_n) values obtained varied from 1.2 to 1.7. The linear increase of the number average molecular weight (M_n) of the copolymers as a function of the

TABLE 2. Crystallinity Data for Poly(LLA-HEMA) Copolymers

Polymer	Mol% LLA/HEMA	% Crystallinity (II scan)
Polylactide[a]	100/0	59.8
PLLA-12[b]	100/0	47.6
P(LLA-HEMA)	99/1	60.1
	98/2	58.5
	96/4	70.7
	94/6	63.9
	92/8	61.6
	90/10	55.4

[a]Polylactide reference material (Boehringer).
[b]Mol ratio LLA/stannous octoate = 133.

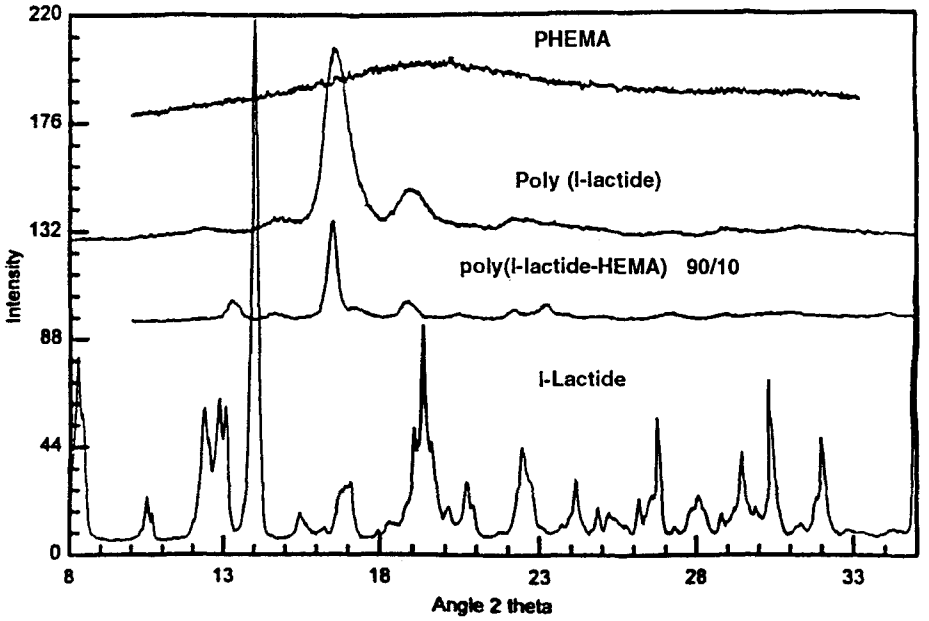


FIG. 4. Typical WAXS spectra of P(LLA-HEMA).

TABLE 3. Glass Transition Temperatures for P(DLLA-HEMA) Copolymers

Polymer	Mol% composition (LLA/HEMA)	T_g, °C
DLH-98	98/2	43.4
DLH-96	96/4	36.3
DLH-94	94/6	37.1
DLH-92	92/8	34.9

TABLE 4. Effect of Stereochemical Composition on Thermal Properties[a]

Polymer	Mol% L-/D,L-lactide	T_g, °C, 2nd	T_m, °C 1st	T_m, °C 2nd	ΔH_m, J/g 1st	ΔH_m, J/g 2nd
LLAH 90/10	100/0	35.7	146	142	48.3	43.6
DLLAH-10	95/10	35.8	114	112	48.6	34.6
DLLAH-20	90/20	40.9	117	—	32.9	—
DLLAH-30	85/30	40.0	104	—	27.6	—
DLLAH-40	80/40	43.5	—	—	—	—

[a] —: Small transition observed.

TABLE 5. Molecular Weight Data for P(LLA-HEMA) copolymers

Polymer	Mol% HEMA	Mol ratio LLA/HEMA	M_n (theory)	M_n	M_w	MWD
PLLA-12	0	133[a]	19,169	19,368	32,790	1.69
PLLAH-1	1	95.3	13,864	11,431	17,124	1.49
PLLAH-2	2	49.0	7,191	7,003	8,629	1.23
PLLAH-4	4	24.0	3,588	4,946	6,320	1.28
PLLAH-6	6	15.5	2,363	2,042	3,554	1.74
PLLAH-8	8	11.2	1,743	1,772	2,884	1.60
PLLAH-10	10	8.99	1,425	1,497	1,944	1.30

[a]LLA/stannous octoate mol ratio.

[LLA]/[HEMA] is illustrated in Fig. 5. It appears therefore that ring-opening polymerization of PLLA initiated with HEMA/stannous octoate proceeds without significant side reactions. Typical for anionic living polymerization reactions, the foregoing results suggest that HEMA serves as a true initiator of PLLA.

Optical Rotation and Circular Dichroism Measurements

One of the objectives of our study was to perform copolymerization of L-/D,L-lactide with HEMA and investigate the thermal properties and possible effects on polymer degradation. Further, an important consideration of choice of stannous octoate as catalyst was the fact that retention of stereochemical purity during conversion of monomer to polymer is high. The specific optical rotation measurements of the P(LLA-HEMA) copolymers are summarized in Table 6. Also reported is the

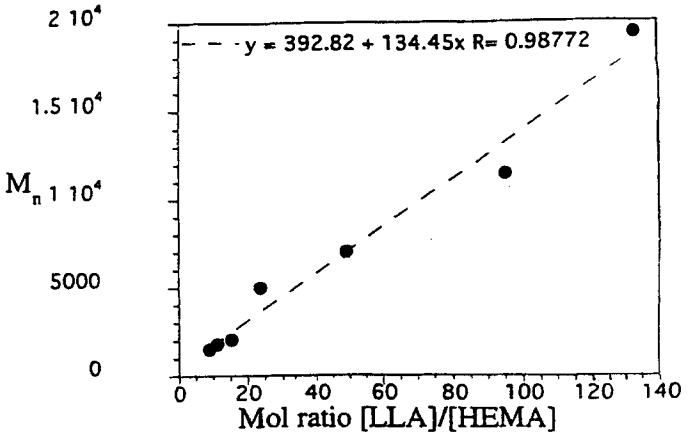


FIG. 5. Dependence of M_n on the [LLA]/[HEMA] mol ratio.

TABLE 6. Specific Optical Rotation Data for P(LLA-HEMA) Copolymers

Polymer	Mol% HEMA	$[\alpha]^a$	$\frac{[\alpha_{experiment}]}{[\alpha_{literature}{}^c]} \times 100$
Monomers:			
L-Lactide		-275^b	97
D,L-Lactide		nd[d]	nd
Polymers:			
PLLA-12	100/0	−161	93
PLLA-13	100/0	−156	90
PLLAH-1	99/1	−167	96
PLLAH-2	98/2	−165	95
PLLAH-4	96/4	−154	89
PLLAH-6	94/6	−149	86
PLLAH-8	92/8	−157	90
PLLAH-10	90/10	−160	92

[a]Specific optical rotation: deg·dm^{-1}·g^{-1}·100 mL.

[b]Literature value at 20°C in toluene (−285).

[c]Literature data for 100% optically pure PLLA = 173.5 [17, 18].

[d]nd = not detected.

percent retention of stereochemistry of the copolymers evaluated using the specific optical rotation value of 173.3 reported for 100% optically pure PLLA [17, 18].

The optical rotation measurements as a function of stereochemical composition of the P(L/DLLA-HEMA) macromonomers are shown in Table 7. It is evident that a gradual decrease in optical rotation results upon addition of 10 to 40 mol% D,L-lactide units. The decrease of specific optical rotation measurements is caused by minute changes of the stereochemical structure of PLLA as a result of the addition of racemic lactide. Although specific optical rotation measurements may

TABLE 7. Effect of Stereochemical Composition on Optical Rotation

Polymer	Mol% L-/D,L-lactide	$[\alpha]^a$	$\frac{[\alpha_{experiment}]}{[\alpha_{literature}]} \times 100$
LLAH 90/10	100/0	−160	92
DLLAH-10	95/10	−146	84
DLLAH-20	90/20	−125	72
DLLAH-30	85/30	−120	69
DLLAH-40	80/40	−86.9	50

[a]Specific optical rotation: deg·dm^{-1}·g^{-1}·100 mL.

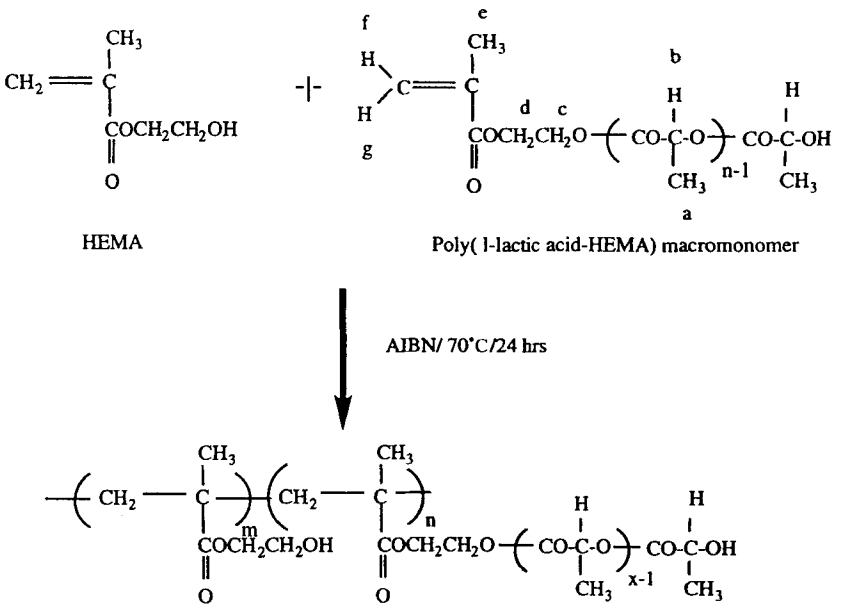
be considered a powerful tool for verification of optical purity of polymers, circular dichroism (CD) or optical rotatory dispersion (ORD) can be used effectively for precise determination of purity using small amount of sample.

Circular dichroism measurements provide additional information on the optical behavior of optically active polymer materials. The CD spectra of P(LLA-HEMA) macromonomers are shown in Fig. 6. All the poly(L-lactic acid-HEMA) macromonomers and optically pure PLLA homopolymer showed a positive CD band, suggesting a similar stereochemical structure. In contrast, no CD band was observed for amorphous poly(D,L-lactic acid). On the basis of CD and specific optical rotation measurements our study demonstrates that no significant racemization occurs for the P(LLA-HEMA) macromonomers and PLLA prepared using stannous 2-ethyl hexanoate catalyst.

Copolymerization of HEMA with Poly(LLA-HEMA) Macromonomers

The incorporation of hydrophilic systems such as HEMA provides one possibility of modulating the rates of polymer degradation and swelling properties of the poly(LA-HEMA) macromonomers by manipulating the hydrophilic-hydrophobic balance. To illustrate this approach (Scheme 2), copolymerization of HEMA with poly(LLA-HEMA) macromonomer was investigated using azo-2,2′-bis(isobutyronitrile) (AIBN) as a free radical initiator to obtain the corresponding "graft" copolymers.

^{1}H-NMR analysis of the "graft" copolymers revealed the disappearance of the characteristic HEMA double bond signals at δ 6.10 and 5.58 corresponding to proton types f and g, respectively. Also, FT-IR analysis confirmed the disappear-



SCHEME 2. Synthesis of poly(HEMA-*graft*-(lactic acid-HEMA) copolymers.

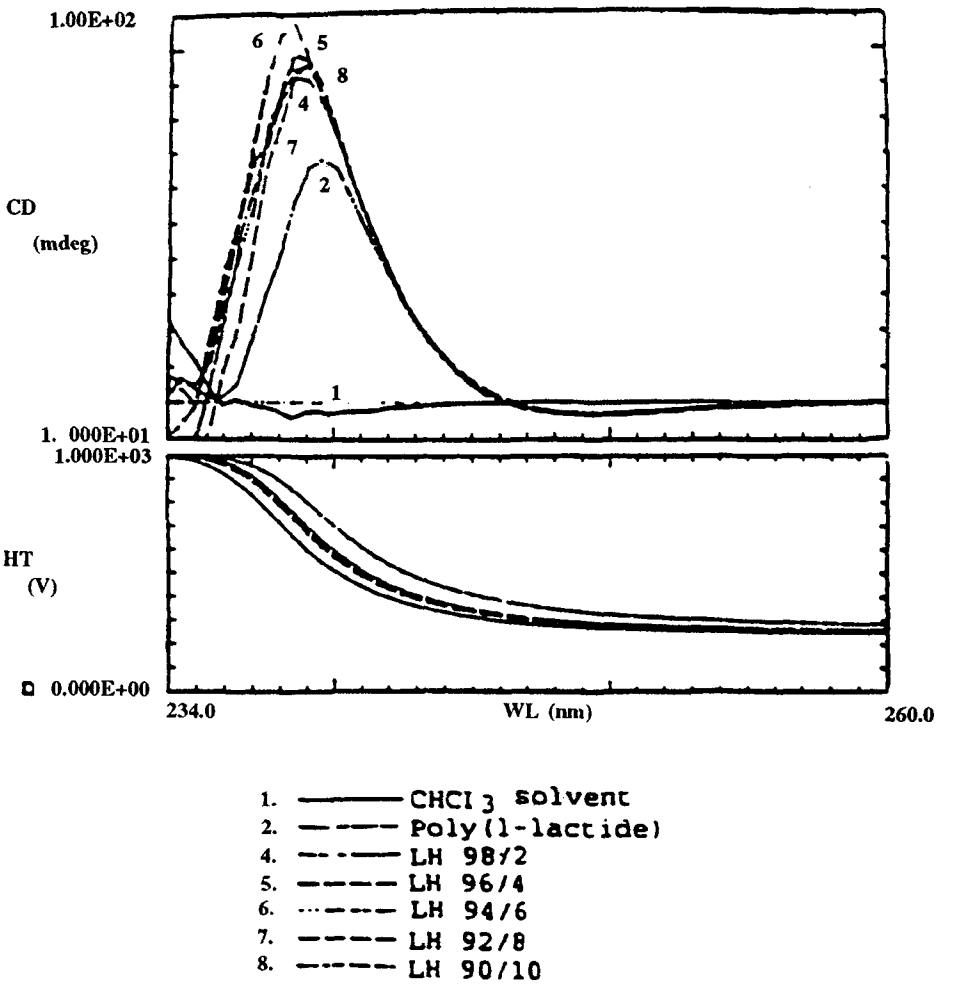


FIG. 6. Circular dichroism spectra of P(LLA-HEMA).

ance of the HEMA C=C absorption band at 1639 cm^{-1}. The results of DSC analysis of HEMA/P(LLA-HEMA) graft copolymer of 50/50 wt% composition are presented in Table 8.

The data presented in Table 8 shows that whereas the melting temperatures of the graft copolymers do not vary much, the heat of fusion values decrease progressively from 43.6 (macromonomer) to 8.19 J/g with increasing HEMA comonomer (50 wt%). The results of the second calorimetric scan are indicative of the decreasing crystallinity of the graft copolymers with increasing HEMA content. Only one glass transition temperature was observed for the graft copolymers intermediate between that of the macromonomer (~ 35.7°C) and PHEMA (~ 107°C).

TABLE 8. DSC Data of HEMA/P(LLA-HEMA)[a] "Graft" Copolymers[b]

		Graft copolymer type		
Parameter	P(LLA-HEMA)[a]	1[c]	2[d]	3[e]
I Scan:				
T_m	146	141	142	139
H_f	48.3	36.4	11.8	19.9
II Scan:				
T_g	35.7	48.3	51.0	50.7
T_m	142	140	144	144
H_f	43.6	20.7	8.19	8.46

[a]P(LLA-HEMA) macromonomer (9 mol% HEMA).
[b]Temperature in °C and enthalpy in J/g.
[c]HEMA/P(LLA-HEMA)/AIBN (81/18/1 wt%).
[d]HEMA/P(LLA-HEMA)/AIBN (49.9/50/0.1 wt%).
[e]HEMA/P(LLA-HEMA)/AIBN (49.5/49.5/1 wt%).

CONCLUSIONS

Poly(LA-HEMA) copolymers have been synthesized and characterized. The hydrophobic nature of PLA may be modified by HEMA incorporation to obtain the desired hydrophilic-hydrophobic balance, an important consideration in biomedical applications. The specific optical rotation and circular dichroism measurements provide evidence of optical purity of the materials prepared in our study. By varying the stereochemical composition, amorphous and semicrystalline polymers are obtained. It is anticipated that polymer degradation may be controlled and tailored for target biomedical applications. The effects of processing conditions on the properties and morphologies of the P(LA-HEMA) macromonomers, degradation, and network formation with different vinylic or acrylic systems and potential applications are being studied and will be reported elsewhere.

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