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Surface biodegradable copolymers — poly(D,L-lactide-co-1-methyl-1,3-trimethylene carbonate) and poly(D,L-lactide-co-2,2-dimethyl-1,3-trimethylene carbonate): preparation, characterization and biodegradation characteristics *in vivo*

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Novel surface biodegradable copolymers, poly(D,L-lactide-co-1-methyl-1,3-trimethylene carbonate) (PLMCA) and poly(D,L-lactide-co-2,2-dimethyl-1,3-trimethylene carbonate) (PLDMCA), have been synthesized by ring-opening polymerization with Sn(Oct)$_2$ as catalyst. The copolymers were characterized by ^{1}H n.m.r., ^{13}C n.m.r. and d.s.c. Water content and static contact angle of distilled water on the polymer surface were used to evaluate the hydrophobicity of the copolymers. Samples were implanted in rats to observe degradation characteristics. It was found that, in both the PLMCA and the PLDMCA copolymer system, the surface biodegradation characteristics *in vivo* were related to polymer hydrophobicities, which mainly depended on the copolymer compositions. The degradation of PLMCA and PLDMCA having a smaller ester fraction became a typical surface reaction. These copolymers may be useful in protein delivery systems. © 1998 Elsevier Science Ltd. All rights reserved.

(Keywords: poly(D,L-lactide-co-1-methyl-1,3-trimethylene carbonate); poly(D,L-lactide-co-2,2-dimethyl-1,3-trimethylene carbonate); polymer surface biodegradation)

INTRODUCTION

With the development of biotechnology, many peptides and proteins have been refined[1]. But, considering their unstability in the body, how to maintain their bioactivity during the release process has become a key problem in protein release systems[2]. Recently, we proposed that using surface biodegradable polymers as protein matrix may overcome this problem[3,4]. When a polymer with a high hydrophobicity character and unstable chemical bonds in the polymer main chain is mixed with protein and made into a device, the matrix degrades only at the surface and the protein in the surface layer diffuses out simultaneously. On the other hand, the protein inside the matrix remains in a stable solid form because of low water permeability in the highly hydrophobic polymer. Thus protein bioactivity may be maintained in the drug release process. We have prepared several novel copolymer systems with surface biodegradable characters, and evaluated the protein bioactivity using these copolymers as matrices. In this paper, we wish to report some preliminary results for PLMCA and PLDMCA on preparation and biodegradation properties *in vivo*.

EXPERIMENTAL

Monomers

1-methyl-1,3-trimethylene carbonate (MCA) and 2,2-dimethyl-1,3-trimethylene carbonate (DMCA) were synthesized

according to the literature[5]. A mixture of 1.0 mol of 1,3-propanediol, 1.1 mol of ethyl carbonate and 0.5 g of sodium metal was heated to 160°C and ethyl alcohol was removed by distillation. When approximately the theoretical amount of alcohol had been collected, the residue was taken up in an equal volume of benzene, washed with water, dried over calcium chloride and then distilled. DMCA was recrystallized from absolute ether (m.p. 110–111°C), MCA was redistilled (b.p. 100–105°C/0.8 torr).

Lactide (LA) was prepared by a method similar to that described by Gilding and Reed[6]: 500 g lactic acid was mixed with 2–5 wt% zinc oxide in a three-necked flask and the temperature raised to 120°C. As the rate of water elimination fell, the temperature was increased to 180°C and the pressure reduced gradually from 760 to 20 torr over a period of 4–6 h. When no more water was evolved, the vacuum was increased to 0.5–1.0 torr. The crude product was distilled out and then recrystallized from ethyl acetate three times. White crystalline LA with a melting point of 125–127°C was obtained.

Scheme 1 shows the synthesis of monomers 1-methyl-1,3-trimethylene carbonate (MCA), 2,2-dimethyl-1,3-trimethylene carbonate (DMCA) and lactide (LA), and copolymers (PLMCA, PLDMCA).

Copolymerization

Poly(D,L-lactide-co-1-methyl-1,3-trimethylene carbonate) (PLMCA) and poly(D,L-lactide-co-2,2-dimethyl-1,3-trimethylene carbonate) (PLDMCA) were copolymerized in bulk. Monomers and catalyst in petroleum ether solution

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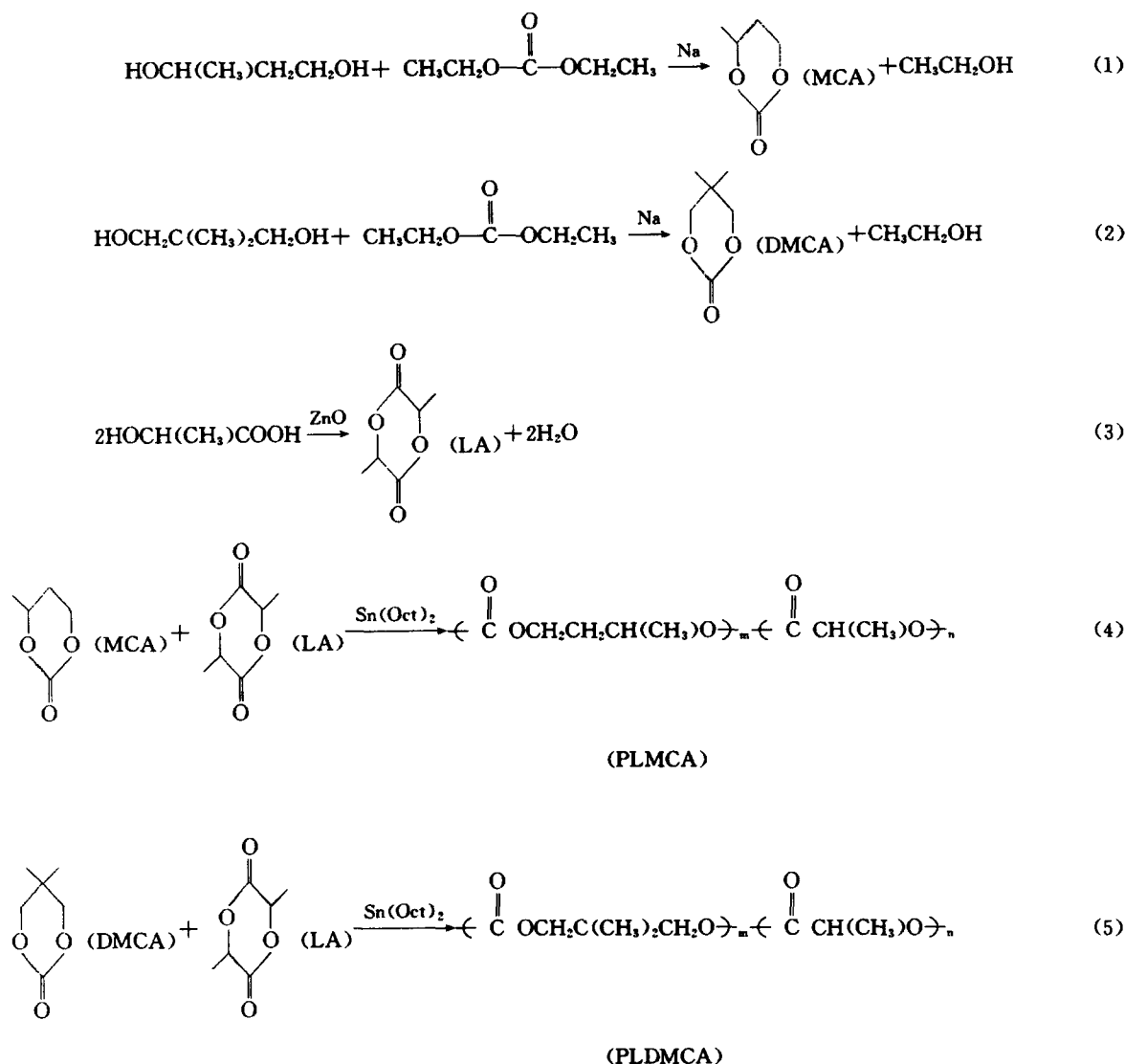
Scheme 1. Synthesis of monomers (1-methyl-1,3-trimethylene carbonate (MCA), 2, 2-dimethyl-1,3-trimethylene carbonate (DMCA) and lactide (LA)), and copolymers (PLMCA,PLDMCA)

were introduced to a well cleaned and dried vessel. The solvent was removed under vacuum, then the vessel was heated to 140°C and maintained at that temperature for 36 h. The products was dissolved in CH_2Cl_2 and precipated from methanol. The molecular weight of the polymers was estimated by gel permeation chromatography (g.p.c., Waters 208). Samples were eluted in THF at 25°C at a flow rate of 1.5 ml min^{-1} through 10^3, 10^4 and 10^5 Å Waters ultrastatyragel columns.

N.m.r. measurements

A JEOL 90Q instrument was employed for n.m.r. measurements using $CDCl_3$ as solvent. ^1H n.m.r. measurements were conducted in 5 mm o.d. sample tubes with internal Me_4Si as shift reference at 89.55 MHz, and ^{13}C n.m.r. measurements were made in 10 mm o.d. sample tubes at 22.49 MHz.

D.s.c. measurements

Samples of 10–15 mg were heated to melting in aluminium pans with inverted lids on a Perkin Elmer DSC-7 Thermal Analyzer at a heating rate of 20°C min^{-1}. The instrument was calibrated with cyclohexane and indium prior to use.

Polymer hydrophobicity evaluation

Water content and static contact angle of distilled water on the polymer surface were used to evaluate the hydrophobicity. Water content was defined as the percentage of water in the wet polymer. It was measured gravimetrically after the polymer had been immersed in distilled water to equilibrium at room temperature. The static contact angle was measured by a contact angle meter (JY-82). A polymer membrane about 2 μm thick was made on a silanized glass microscopy slide by the casting method. Static contact angles were measured at 25°C on profiles of sessile drops using a microscope fitted with a goniometer eyepiece, with magnification 20×. Readings were taken within 10–15 s, average drop size was 0.05 ml. Angles were measured on six different regions of each polymer surface and the results averaged.

Polymer degradation

Samples of cylindrical shape (2.5 mm diameter, 7 mm length) were made by compression in a mould at 40°C for 5 min under a pressure of 100 kg cm^{-2}. A degradation test *in vivo* was carried out in rats. Polymer samples were weighed and sterilized by dipping in 70% ethanol solution before being implanted subdermally in adult ICH rats in the

Table 1 Evaluation of hydrophobicity of PLMCA and PLDMCA systems[a]

Polymer	PLMCA15	PLMCA30	PLMCA50	PLDMCA20	PLDMCA30	PLDMCA50
Water content (wt%)	1.35 (± 0.02)	1.61 (± 0.02)	2.20 (± 0.02)	0.80 (± 0.02)	1.00 (± 0.02)	1.60 (± 0.02)
Contact angle (°)	63 (± 2)	58 (± 2)	38 (± 2)	74 (± 2)	70 (± 2)	63 (± 2)

[a]Water contents were measured gravimetrically after samples ($n = 2$) had been immersed in distilled water to equilibrium at room temperature. Static contact angles were measured by a contact angle meter at 25°C, average drop size was 0.05 ml and the readings were taken within 10~15 s ($n = 6$)
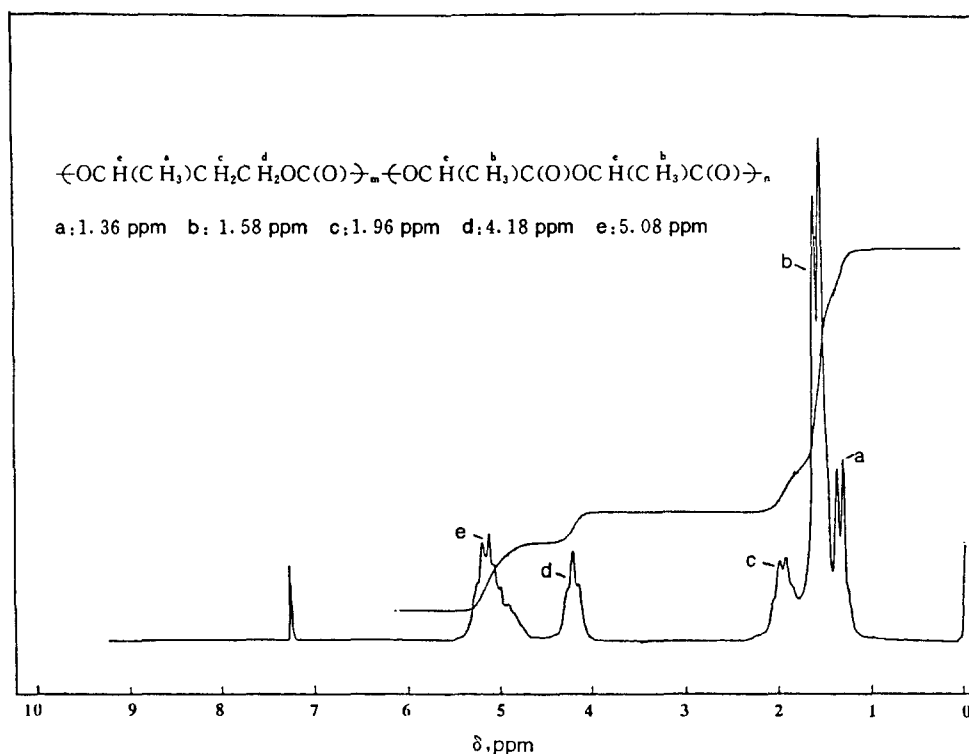
Table 2 T_g values of PLMCA and PLDMCA systems[a]

Polymer	PLMCA15	PLMCA30	PLMCA50	PLDMCA20	PLDMCA30	PLDMCA50
T_g (°C)	− 5.0	4.4	16.1	− 3.8	10.5	24.1

[a]Measured on a Perkin Elmer DSC-7 Thermal Analyzer at a heating rate of 20°C min^{-1}

Table 3 Degradation of PLMCA system *in vivo*[a]

PLMCA		PLMCA15		PLMCA30		PLMCA50	
		M_n	M_n/M_{n0} (%)	M_n	M_n/M_{n0} (%)	M_n	M_n/M_{n0} (%)
10 days	surface	15 447	99.0	18 218	98.1	14 005	73.7
	bulk	15 603	100.0	18 404	99.1	17 085	89.9
20 days	surface	13 107	84.0	14 260	76.8	12 733	67.0
	bulk	15 261	97.8	18 011	97.0	16 153	85.0
40 days	surface	11 545	74.0	12 591	67.8	11 762	61.9
	bulk	14 996	96.1	17 494	94.2	13 226	69.6
60 days	surface	10 249	65.7	10 826	58.3	10 510	55.3
	bulk	14 823	95.0	16 918	91.1	11 573	60.9

[a]M_n was determined by g.p.c. in THF at 25°C. M_{n0} of PLMCA15, PLMCA30 and PLMCA50 were 15 603, 18 570 and 19 004, respectively

$\{OC\ \overset{a}{H}(C\ \overset{a}{H_3})C\ \overset{c}{H_2}C\ \overset{d}{H_2}OC(O)\}_m\{OC\ \overset{e}{H}(C\ \overset{b}{H_3})C(O)OC\ \overset{e}{H}(C\ \overset{b}{H_3})C(O)\}_n$

a : 1. 36 ppm   b : 1. 58 ppm   c : 1. 96 ppm   d : 4. 18 ppm   e : 5. 08 ppm

Figure 1 ^{1}H n.m.r. spectrum and assignment of poly(D,L-lactide-*co*-1-methyl-1,3-trimethylene carbonate) (PLMCA50), measured in CDCl$_3$ at 30°C

scapular area lateral to the dorsal midline. At suitable time intervals the animals were sacrificed and the polymers were recovered. The samples were freed from adhering tissues, rinsed with distilled water and dried. Molecular weights of the inner bulk and surface layer were measured by g.p.c.

RESULTS AND DISCUSSION

Polymer synthesis

According to previous work[4], the copolymerization conditions were set up as follows: catalyst concentration, 1×10^{-2}–1×10^{-3} mol%; copolymerization temperature,

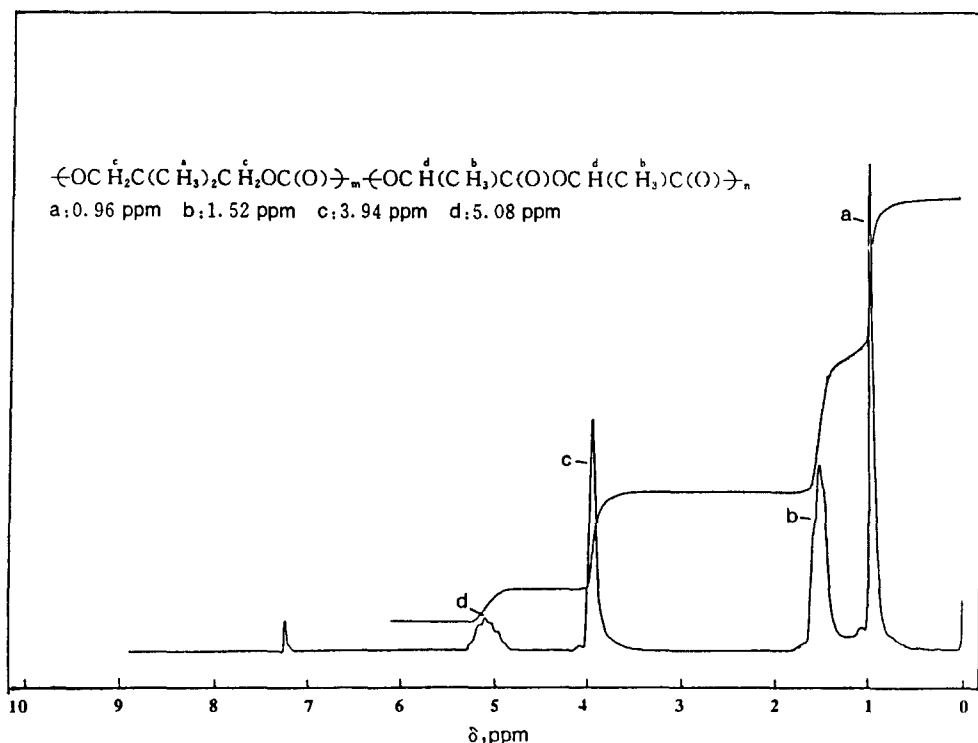**Figure 2** ^1H n.m.r. spectrum and assignment of poly(D,L-lactide-*co*-2,2-dimethyl-1,3-trimethylene carbonate) (PLDMCA50), measured in $CDCl_3$ at 30°C
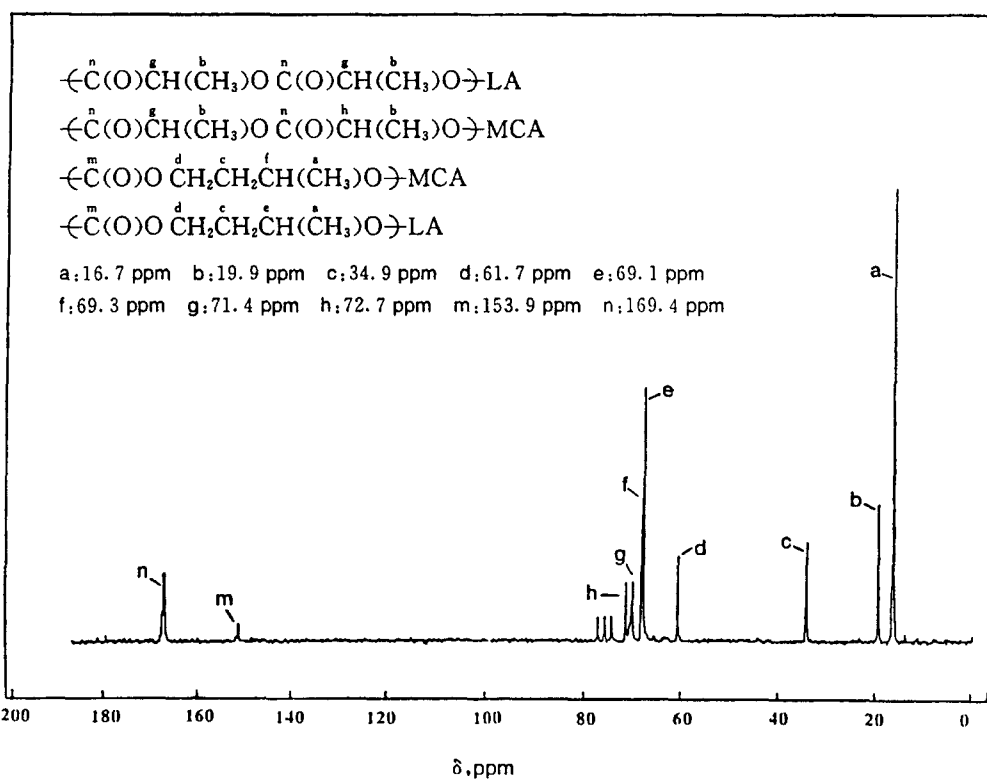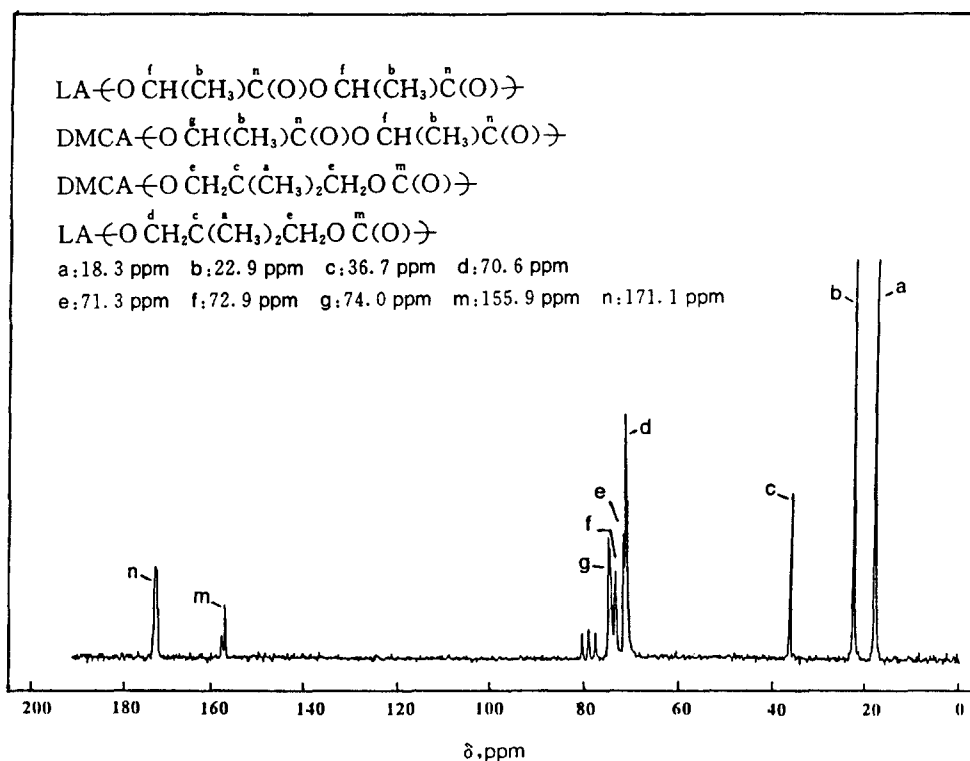

Figure 3 ^{13}C n.m.r. spectrum and assignment of poly(D,L-lactide-*co*-1-methyl-1,3-trimethylene carbonate) (PLMCA50), measured in $CDCl_3$ at 30°C

140°C; reaction time, 36 h. The polymerization yields of PLMCA and PLDMCA were about 70–80%. All the copolymers (PLMCA15, PLMCA30, PLMCA50, PLDMCA20, PLDMCA30, PLDMCA50, the numbers representing the approximate LA mole percentage in the copolymers) were soluble in dichloromethane, trichloromethane, tetrahydrofuran, dioxane etc., but insoluble in alcohol and ether. M_n values were about 15 000–20 000; the MWD values were in the range of 1.5–2.0. *Figures 1* and *2*

are the ^1H n.m.r. spectra of PLMCA and PLDMCA copolymers, respectively. In comparison with the spectra of monomers, we can assign the peaks easily. In *Figure 1*: 1.36 ppm (–CH_3 of MCA), 1.58 ppm (–CH_3 of LA), 1.96 ppm (–CH_2– of MCA), 4.18 ppm (–OCH_2– of MCA) and 5.08 ppm (–OCH< of MCA and LA); in *Figure 2*: 0.96 ppm (–CH_3 of DMCA), 1.52 ppm (–CH_3 of LA), 3.94 ppm (–OCH_2– of DMCA) and 5.08 ppm (–OCH< of LA). ^{13}C n.m.r. spectra of PLMCA and PLDMCA are

Figure 4 ^{13}C n.m.r. spectrum and assignment of poly(D,L-lactide-*co*-2,2-dimethyl-1,3-trimethylene carbonate) (PLDMCA50), measured in CDCl$_3$ at 30°C
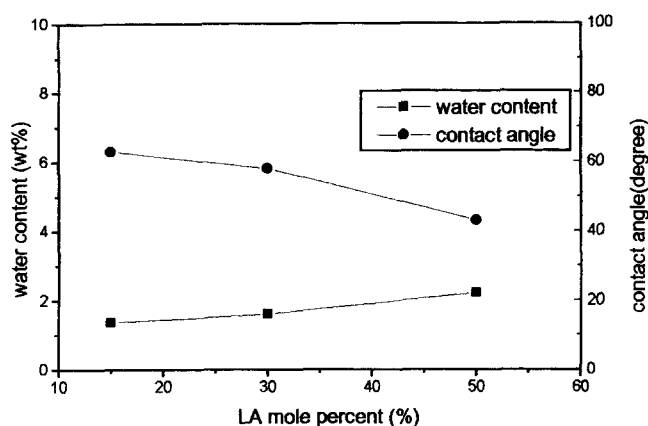
Figure 5 The relationship between polymer hydrophobicity and polymer composition for the PLMCA system. Water contents and static contact angles were measured in the conditions mentioned in *Table 1*
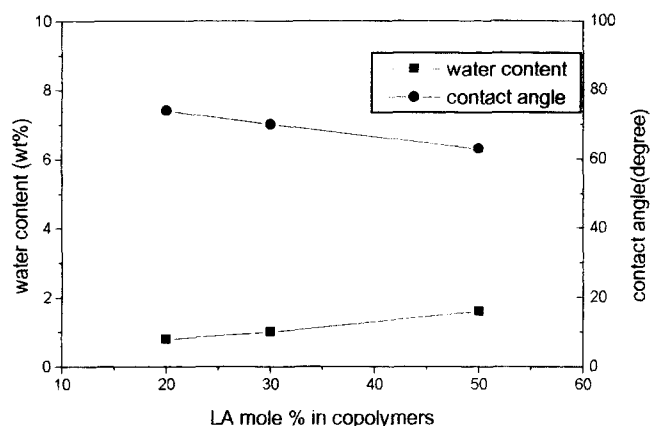

Figure 6 The relationship between polymer hydrophobicity and polymer composition for the PLDMCA system. Water contents and static contact angles were measured in the conditions mentioned in *Table 1*

shown in *Figures 3* and *4*, respectively. In *Figure 3*, we assigned the peaks as: 16.7 ppm (–CH$_3$ of MCA), 19.9 ppm (–CH$_3$ of LA), 34.9 ppm (–CH$_2$– of MCA), 61.7 ppm (–OCH$_2$– of MCA), 69.1 ppm and 69.3 ppm (–OCH < of MCA), 71.4 ppm and 72.7 ppm (–OCH< of LA), 153.9 ppm (–C(=O)– of MCA units) and 169.4 ppm (–C(=O)– of LA). *Figure 4* shows the ^{13}C n.m.r. spectrum of PLDMCA copolymer: 18.3 ppm (–CH$_3$ of DMCA), 22.9 ppm (–CH$_3$ of LA), 36.7 ppm (>C< of DMCA), 70.6 ppm and 71.3 ppm (–OCH$_2$– of DMCA), 72.9 ppm and 74.0 ppm (–OCH< of LA), 155.9 ppm (–C(=O)– of DMCA) and 171.1 ppm (–C(=O)– of LA).

According to ^{1}H n.m.r. analysis, we can calculate the reactivity ratios of PLMCA and PLDMCA copolymer systems. The reactivity ratios *r* were calculated from the following equation:

$$M/N = (r_m m/n + n)/(r_n n/m + m) \qquad (6)$$

where *m* and *n* are feed compositions of the two

components, *M* and *N* are compositions in the copolymers as determined by ^{1}H n.m.r. The values of reactivity ratios of PLMCA and PLDMCA copolymer systems were obtained as $r_{LA} = 1.58$, $r_{MCA} = 0.48$; $r_{LA} = 1.93$, $r_{DMCA} = 0.59$, respectively, which indicated that LA was more active than MCA or DMCA in their copolymerizations.

Polymer hydrophobicity

The water contents and static contact angles of PLMCA and PLDMCA copolymers are listed in *Table 1*. *Figures 5 and 6* further express the linear relationship between hydrophobicity and copolymer composition in both PLMCA and PLDMCA systems. It can be seen that the hydrophobicity of the copolymers decreased with increasing LA fraction in the copolymers; and, with the same LA content, PLMCA copolymers showed more hydrophilic character than that of the corresponding PLDMCA copolymers.

The d.s.c. results of the two copolymer systems are given
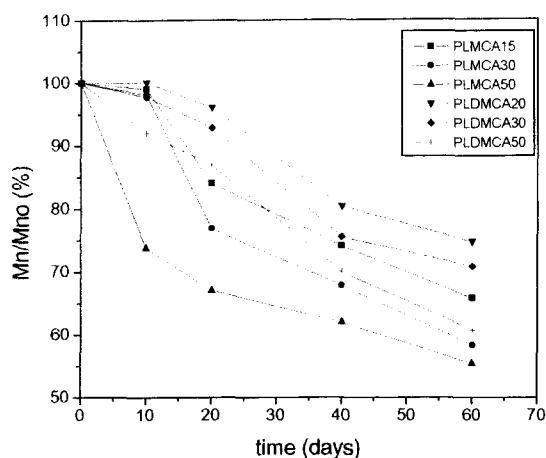
Figure 7 Molecular weight changes of surface layer for PLMCA and PLDMCA copolymers
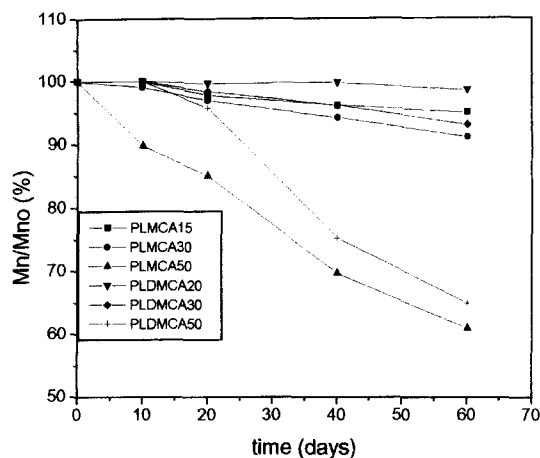
Figure 8 Molecular weight changes of inner bulk for PLMCA and PLDMCA copolymers

Table 4 Degradation of PLDMCA system in *vivo*[a]

PLDMCA		PLDMCA20		PLDMCA30		PLDMCA50	
		M_n	M_n/M_{n0} (%)	M_n	M_n/M_{n0} (%)	M_n	M_n/M_{n0} (%)
10 days	surface	13 980	100.0	25 689	97.7	20 725	92.0
	bulk	13 986	100.0	26 358	100.0	22 531	100.0
20 days	surface	13 427	96.0	25 304	92.8	19 582	86.9
	bulk	13 943	99.7	25 936	98.4	21 585	95.8
40 days	surface	11 231	80.3	19 900	75.5	15 772	70.0
	bulk	13 955	99.8	25 330	96.1	16 939	75.2
60 days	surface	10 434	74.6	18 654	70.7	13 680	50.7
	bulk	13 795	98.6	24 539	93.1	14 623	64.9

[a] M_n was determined by g.p.c. in THF at 25°C. M_{n0} of PLDMCA20, PLDMCA30 and PLDMCA50 were 13 986, 26 358 and 22 531, respectively

Table 5 Discrepant degradation between bulk and surface layer for PLMCA and PLDMCA systems[a]

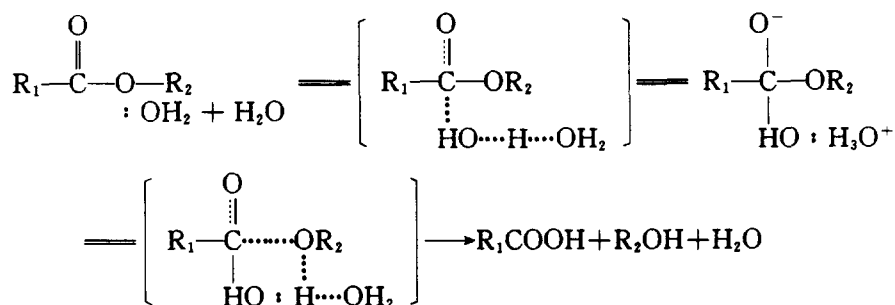|	20 days		40 days		60 days	
	$\Delta M_n/M_{n0}$	M_n/M_{n0}(bulk)	$\Delta M_n/M_{n0}$	M_n/M_{n0}(bulk)	$\Delta M_n/M_{n0}$	M_n/M_{n0}(bulk)
PLMCA15	13.8%	100%	22.1%	96.1%	29.3%	95.0%
PLMCA30	20.2%	97.0%	26.4%	94.2%	32.8%	91.1%
PLDMCA20	3.7%	99.7%	19.5%	99.8%	24.0%	98.6%
PLDMCA30	5.6%	98.4%	20.6%	96.1%	22.4%	93.1%
PLMCA50	18.0%	85.0%	7.7%	69.6%	5.6%	60.9%
PLDMCA50	8.9%	95.8%	5.2%	75.2%	4.2%	64.9%

[a] $\Delta M_n/M_{n0}$ was the discrepant degradation between bulk and surface layer for PLMCA and PLDMCA systems, $\Delta M_n/M_{n0} = M_n/M_{n0}$ (bulk) $- M_n/M_{n0}$ (surface); data were obtained from *Tables 3* and *4*. M_n was determined by g.p.c. in THF at 25°C

in *Table 2*. We can see that all copolymers had only one T_g and no T_m, the value of T_g increasing with increasing LA content. We also can see that the T_g values of the PLMCA system were lower than those of the corresponding PLDMCA system; that is, PLMCA copolymers were more flexible than the corresponding PLDMCA copolymers. This may be attributed to the different stereoscopic effect of MCA and DMCA in polymer chains. The water contents not only depend on the chemical structure but are also related to morphologies of the copolymers. In the miscible state of PLMCA and PLDMCA, we can simply attribute the water contents to the different hydrophobicity caused by a variety of carbonate and ester segments, since the water contents of PLMCA, PLDMCA and PLA were 0.95, 0.34 and 5.20%, respectively.
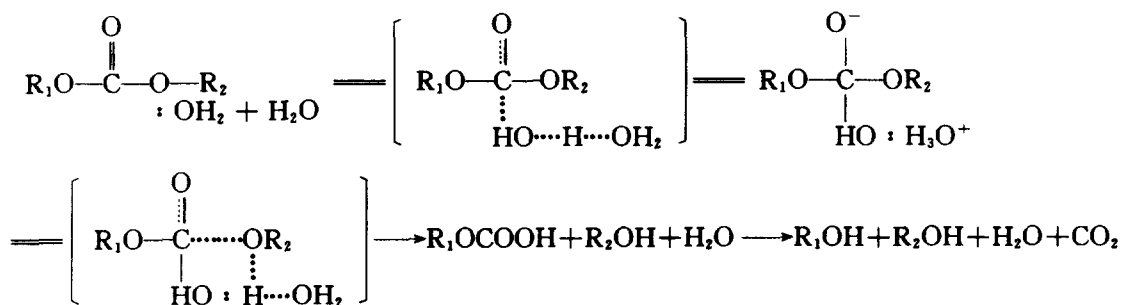
Polymer degradation

The degradation of PLMCA and PLDMCA systems *in vivo* was measured by changes in molecular weight of the

bulk polymer and the outer surface layer. The recovered samples were extracted with chloroform for 3–5 min to selectively separate the surface fraction (about 3 wt% of the sample). Control experiments showed that chloroform, a poor solvent for the two copolymer systems, slowly dissolved the surface layer of the polymer and did not selectively leach the oligomeric components. The results are shown in *Table 3* and *Table 4*. The data were further analysed in order to understand the polymer degradation characteristics. *Figures 7* and *8* show the MW changes of the bulk and the surface layer for the PLMCA and PLDMCA systems, respectively. For either bulk or surface layer, the degradation rates of PLMCA copolymers were all faster than those of the corresponding PLDMCA copolymers. It is well known that the degradation of polycarbonate and polyester are recognized as mainly a process of hydrolysis in aqueous solution[7,8]. The hydrolysis mechanism can be demonstrated as in *Schemes 2* and *3*, which show the degradation processes for polyester and

$$R_1-C(=O)-O-R_2 : OH_2 + H_2O \rightleftharpoons \left[R_1-C(=O)-OR_2 ; HO\cdots H\cdots OH_2 \right] \rightleftharpoons R_1-C(O^-)-OR_2 ; HO : H_3O^+$$

$$\rightleftharpoons \left[R_1-C(=O)\cdots OR_2 ; HO : H\cdots OH_2 \right] \longrightarrow R_1COOH + R_2OH + H_2O$$

Scheme 2. Polyester degradation process

$$R_1O-C(=O)-O-R_2 : OH_2 + H_2O \rightleftharpoons \left[R_1O-C(=O)-OR_2 ; HO\cdots H\cdots OH_2 \right] \rightleftharpoons R_1O-C(O^-)-OR_2 ; HO : H_3O^+$$

$$\rightleftharpoons \left[R_1O-C(=O)\cdots OR_2 ; HO : H\cdots OH_2 \right] \longrightarrow R_1OCOOH + R_2OH + H_2O \longrightarrow R_1OH + R_2OH + H_2O + CO_2$$

Scheme 3. Polycarbonate degradation process

polycarbonate, respectively.

Polyester degradation rate $= K_1[H_2O][COOH][ester]$ (7)

Polycarbonate degradation rate $= K_2[H_2O][carbonate]$ (8)

The degradation rates of PLMCA copolymers were faster than those of the corresponding PLDMCA. This can be mainly attributed to the higher hydrophilicity of PLMCA copolymers; that is, the higher water concentration ([H₂O]) in the PLMCA copolymers which facilitated the degradation of both ester and carbonate segments.

On the other hand, the copolymer hydrophilicity enhanced with increasing LA content, the degradation rates of PLMCA and PLDMCA rising as shown in *Figures 7* and *8*, respectively. The degradation process of polyester and polycarbonate indicated that polymers containing more LA produced more acidic products, which accelerated the copolymer degradation. This autocatalytic effect is another reason for the faster degradation rate of polymers with higher LA content.

It was found that polymer degradation characteristics changed from surface to bulk degradation when the LA content was increased to 50 mol%. *Table 5* shows the discrepant degradation between bulk and surface layer of polymers at time intervals. The discrepancy of PLMCA15, PLMCA30, PLDMCA20 and PLDMCA30 rose to about 20%–30% while the inner bulk remained almost un-degraded, showing typical surface degradation characteristics[9–12]. But for PLMCA50 and PLDMCA50 the discrepancy between inner bulk and surface layer was very small, which showed the characteristic of bulk degradation. In addition, the bulk degradation of PLDMCA was less than those of corresponding PLMCA copolymers because of their higher hydrophobicity.

CONCLUSIONS

PLMCA and PLDMCA copolymers with different compositions of ester and carbonate segments were synthesized by ring-opening polymerization using stannous octoate as catalyst. The PLMCA and PLDMCA systems were highly hydrophobic copolymers, and the hydrophobicity decreased linearly with increasing LA content. In both systems, differences in hydrophobicity resulted in polymers with different degradation behaviour. The critical composition of transitions from bulk to surface degradation was about 40 mol% of LA content in both PLMCA and PLDMCA systems. The PLMCA copolymers degraded faster than the corresponding PLDMCA copolymers, showing fewer surface degradation characteristics. These materials may be useful in drug delivery systems.

ACKNOWLEDGEMENTS

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