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Structure and morphology of solid lactide–glycolide copolymers from ^{13}C n.m.r., infra-red and Raman spectroscopy

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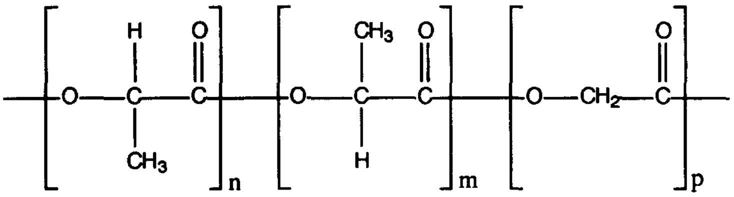
The chemical composition, morphology and configuration of a series of solid lactide–glycolide copolymers (PLA_XGA_Y: X, % L-lactide and Y, % glycolide) were studied by solid state ^{13}C n.m.r., infra-red and Raman spectroscopy. Chemical composition was evaluated from the relative intensities of CH_2 and CH carbon n.m.r. peaks and from the intensity ratio of δCH_2 and $\delta_{as}CH_3$ bending Raman peaks. Relationships with GA% content were compared. Raman spectroscopy appeared more sensitive to the stereochemistry of copolymers than CP/MAS ^{13}C n.m.r.. It allowed discrimination of amorphous $PLA_{42.5}GA_{15}$ from $PLA_{85}GA_{15}$, and $PLA_{37.5}GA_{25}$ from $PLA_{75}GA_{25}$ based on the new band at $\approx 1334\ cm^{-1}$ assigned to δCH bending modes relative to D-LA units. In contrast, solid state ^{13}C n.m.r. did not allow distinguishing the specific L- and D,L-LA unit distribution present in the terpolymers. © 1998 Elsevier Science Ltd. All rights reserved.

(Keywords: lactide-glycolide copolymers; solid state ^{13}C n.m.r)

INTRODUCTION

Aliphatic polyesters based on glycolic and lactic acids (PLA/GA) are the most investigated and advanced bioresorbable polymers used to make biomedical and pharmaceutical devices. They now cover an extensive range of applications such as surgical sutures[1], devices for bone-fracture internal fixation[2] and as controlled drug-delivery systems[3]. The hydrolytic degradation of PLA/GA polymers depends not only on experimental parameters such as pH, ionic strength and temperature, but also on polymer characteristics such as $\bar{M}_w$ molecular weight, chemical composition, and structural properties such as monomer stereochemistry, co-monomer ratio, morphology and configurational structure[4].



$$\left[-O-\overset{H}{\underset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}-\right]_n\left[-O-\overset{CH_3}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}}-\right]_m\left[-O-CH_2-\overset{O}{\overset{\|}{C}}-\right]_p$$

For the sake of clarity, the various PLA/GA polymers and copolymers are currently identified by the acronym PLA_XGA_Y[4] where X is the percentage $n/(n+m+p)$ of L-LA units present in the monomer feed and Y is the percentage $p/(n+m+p)$ of GA units, the percentage in D-LA units being $100-(n+p)$.

Gilding and Reed[5] reported that most of the copolymers are amorphous compounds. In the P(L-LA/GA) series, the composition range corresponding to amorphous compounds extended from 25 to 75% in GA units, whereas in the P(D,L-LA/GA) series, this range varied from 0 to 70%. PLA_X stereocopolymers and PLA_XGA_Y heterocopolymers generally degrade faster than homopolymers[6]. Cutright *et al.*[7] carried out a systematic *in vivo* degradation study on a series of P(L-LA/GA) copolymers: the degradation rate was found to increase as $PGA < PLA_{100} < PLA_{75}GA_{25} < PLA_{50}GA_{50} < PLA_{25}GA_{75}$. Among copolymers of racemic lactide and glycolide, previous studies[8] had shown that the degradation rate increased as $PLA_{85}GA_{15} < PLA_{75}GA_{25} < PLA_{42.5}GA_{15} < PLA_{37.5}GA_{25}$. Therefore, the chirality of lactyl units provides a worthwhile means to adjust bioresorption rates as well as physical and mechanical properties. The early stages of the degradation of semi-crystalline polymers concern primarily amorphous zones, and thus an increase in crystallinity[9–11]. Two classes of PLA/GA copolymers can be distinguished: the first class consists of polymers which can never crystallize during the degradation ($PLA_{42.5}GA_{15}$, $PLA_{37.5}GA_{25}$, $PLA_{25}GA_{50}$ for example). The second can crystallize during degradation ($PLA_{85}GA_{15}$, $PLA_{75}GA_{25}$). For this class, preferential degradation of GA units was observed, resulting in a enrichment in L-LA segments which finally crystallized[12]. A crystalline residue was even detected at the last stage of degradation of PLA_{50}[13], the short residual chains forming a stereocomplex of L-LA and D-LA rich oligomers. All these results demonstrate that chemical, morphological and configurational changes are predominant factors which govern the hydrolytic degradation.

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Many techniques are used to characterize PLA/GA polymers, namely: i.r., d.s.c., SEC, X-ray diffraction, solution and solid state ^{1}H and ^{13}C n.m.r., etc. As reported in previous papers dealing with series of PLA$_X$ homopolymers[14], stereocopolymers[15], and PGA homopolymers[16], Raman vibrational spectroscopy is also a powerful technique for the study of polymer structures because it does not cause or require any sample modification and thus it preserves the morphology. The complete assignment of fundamental vibrations of the two crystalline homopolymers PLA$_{100}$ and PGA has allowed distinction between the bands typical of chain arrangement and those reflecting chain structure and conformation. The spectral comparison of PLA$_{100}$ with PLA$_X$ stereocopolymers has shown that the difference in tacticity between 'preferentially isotactic' poly(D,L-lactide) and 'preferentially syndiotactic' poly(*meso*-lactide)[17] can be detected from the vibrational position of δCH and symmetric δCH$_3$ bending modes.

The aim of this work is to analyze various L-LA/GA and D,L-LA/GA copolymers in the solid state by ^{13}C n.m.r. and vibrational spectroscopy and to show the application of Raman spectroscopy for the analysis of morphology, chemical composition and configurational structure of the PLA/GA family.?tpb=3pt>

EXPERIMENTAL

Materials

Poly(L-lactide-co-glycolide) and poly(D,L-lactide-co-glycolide) were obtained by bulk ring-opening polymerization at 145°C of L-lactide and glycolide, or D,L-lactide and glycolide, in different proportions (25:75, 50:50 and 75:25) using zinc powder as the initiator. Low molecular weight residual compounds were removed by dissolution in acetone and precipitation with methanol. The recovered polymer was vacuum-dried for 1 week and processed by compression moulding (200 bars) to yield 7.5-cm diameter round plates. The resulting plates were then machined to yield parallel-sided specimens according to a process used repeatedly in the past[18]. Relative weight average molecular weights ($\bar{M}_w \approx 100\,000$) were determined by size-exclusion chromatography referred to polystyrene standards.

^{13}C n.m.r. spectra

High-resolution solid-state ^{13}C n.m.r. spectra were measured on a Brucker AM300 spectrometer operating at 75.470 MHz. For CP/MAS spectra, the contact time was 5 ms and the recycle times were 5 s. For MAS without cross-polarization, a 90° pulse of 4–8 μs was used for carbon. All the spectra were recorded at room temperature.

Raman spectra

Raman spectra were obtained with a Jobin-Yvon HG2S spectrometer. The 514.5 nm line of the Spectra Physics 2017 argon ion laser was used as the excitation source. Laser power was 100 mW. The scanning operations and data processing were under the control of a spectralink board and an IBM PC computer. The integration time was 1 s with a scanning increment of 1 cm^{-1} and a bandwidth of 2 cm^{-1}. PLA(s) were analysed under the form of small fragments obtained from the round plates, without any other specific preparation. Spectra were recorded at room temperature after the exposure time necessary to decay the fluorescence.

Infra-red spectra

Infra-red spectra were recorded on a Perkin Elmer 983G spectrometer. Thin films were cast from chloroform solutions onto a KRS5 plate.

RESULTS AND DISCUSSION

^{13}C n.m.r. spectroscopy

Figure 1 shows the CP/MAS ^{13}C n.m.r. spectra obtained for samples of PLA$_{100}$ homopolymer, of PLA$_{50}$ and of PLA/GA copolymers at room temperature and with a contact time of 5 ms. The three rough peaks centered at 17.0, 70.1 and 170.2 ppm were attributed to the methyl, methine and carbonyl carbon resonances corresponding to LA-units. In the partially crystalline PLA$_{100}$, these resonance peaks were split according to the 10$_3$ helical conformation[15]. In PLA$_{50}$, the resonance lines did not present any splitting, in agreement with its amorphous state. The lines due to the methylene carbon resonances of GA-units appeared at

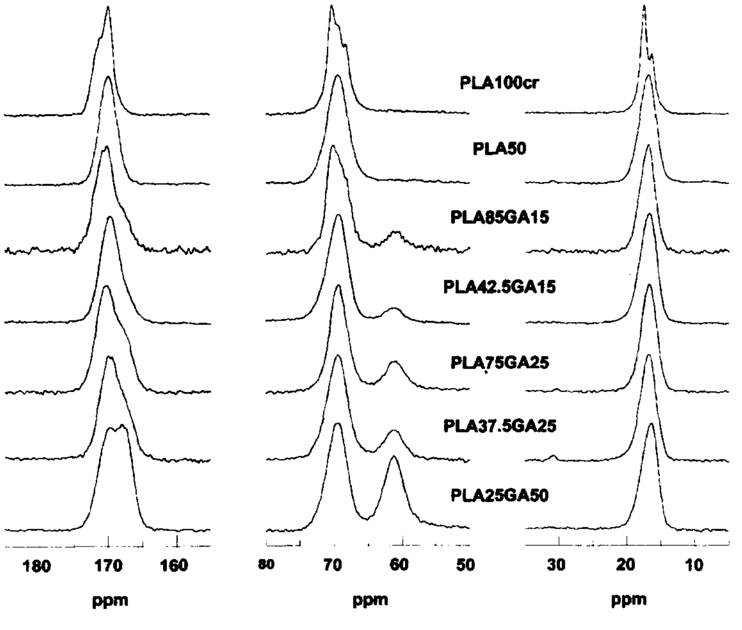

Figure 1 CP/MAS ^{13}C n.m.r. spectra of PLA$_{100}$, PLA$_{50}$, PLA$_X$GA$_Y$ poly(lactic-*co*-glycolic)acids; cr, semi-crystalline

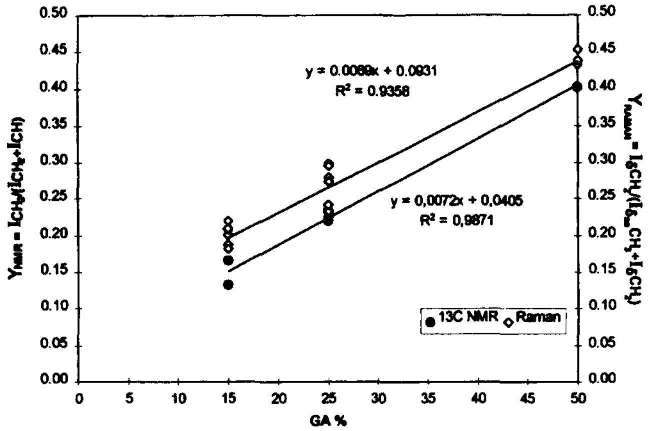

Figure 2 Plot of relative Raman intensity ratio

$$I_{\delta CH_2}/(I_{\delta CH_2}+I_{\delta_{as}CH_3})$$

and relative CP/MAS ^{13}C n.m.r. intensity ratio

$$I_{CH_2}/(I_{CH_2}+I_{CH})$$

versus % GA content

61.3 ppm, and that of carbonyl carbon were well identified at 168.0 ppm in $PLA_{25}GA_{50}$. For the amorphous $PLA_{42.5}GA_{15}$, $PLA_{75}GA_{25}$, $PLA_{37.5}GA_{25}$ and $PLA_{25}GA_{50}$, the methine carbon resonances were observed as symmetric large bands, whereas that of $PLA_{85}GA_{15}$ was asymmetric and resembled that of PLA_{100} homopolymer, suggesting a slight degree of crystallinity. The copolymer composition was evaluated from the intensity ratio of CH_2 and CH carbon peaks (*Figure 2*). The plot of

$$I_{CH_2}/(I_{CH_2}+I_{CH})$$

versus GA% showed a significant linear regression obtained on a series of PLA/GA (three samples by composition) with correlation square $r^2 = 0.987$. However, solid-state ^{13}C n.m.r. did not allow distinguishing the $PLA_{75}GA_{25}$ copolymer from the $PLA_{37.5}GA_{25}$ terpolymer, both being amorphous. Therefore, it was not an accurate technique for analyzing the stereostructures of the chains at room temperature.

Vibrational spectroscopy

The infra-red (*Figure 3*) and Raman spectra (*Figure 4*) of PLA/GA polymers yielded diagnostic bands specific for the functional groups present within the primary structure. These bands depended not only on the copolymer composition and the crystalline structure, but also the configuration. The vibrational analysis (*Table 1*) was based on previous results obtained for PLA_{100}[14] and PGA[16] homopolymers and for stereocopolymers of PLA_{50}[15].

Copolymer composition

The δCH₂ and δCH₃ deformation bands. The δCH_2 band observed at about 1420 cm^{-1} and the $\delta_{as}CH_3$ asymmetric deformation band located at 1452 cm^{-1} in the Raman spectra (*Figure 5*) allowed differentiation of copolymers with different compositions in GA units, as exemplified for 15, 25 and 50% contents in GA units. *Figure 2* shows the variation of the intensity ratio

$$I_{\delta CH_2}/(I_{\delta CH_2}+I_{\delta_{as}CH_3})$$

for the two Raman lines as a function of content in GA% in the $PLA_{85}GA_{15}$, $PLA_{42.5}GA_{15}$, $PLA_{75}GA_{25}$, $PLA_{37.5}GA_{25}$ and $PLA_{25}GA_{50}$. For each of the five copolymers, three samples were analysed. A significant linear regression ($r^2 = 0.936$) was obtained and showed that this ratio is independent of the chirality of the LA monomers. Because the two Raman lines were well separated, the regression line

$$I_{\delta CH_2}/(I_{\delta CH_2}+I_{\delta_{as}CH_3}) = 0.0069\ \mathrm{GA\%} + 0.093$$

provided a rapid and simple method to determine the GA content in PLA/GA polymers.

The skeletal bands. The νCC stretching modes appeared as sharp Raman lines of high intensity. They corresponded

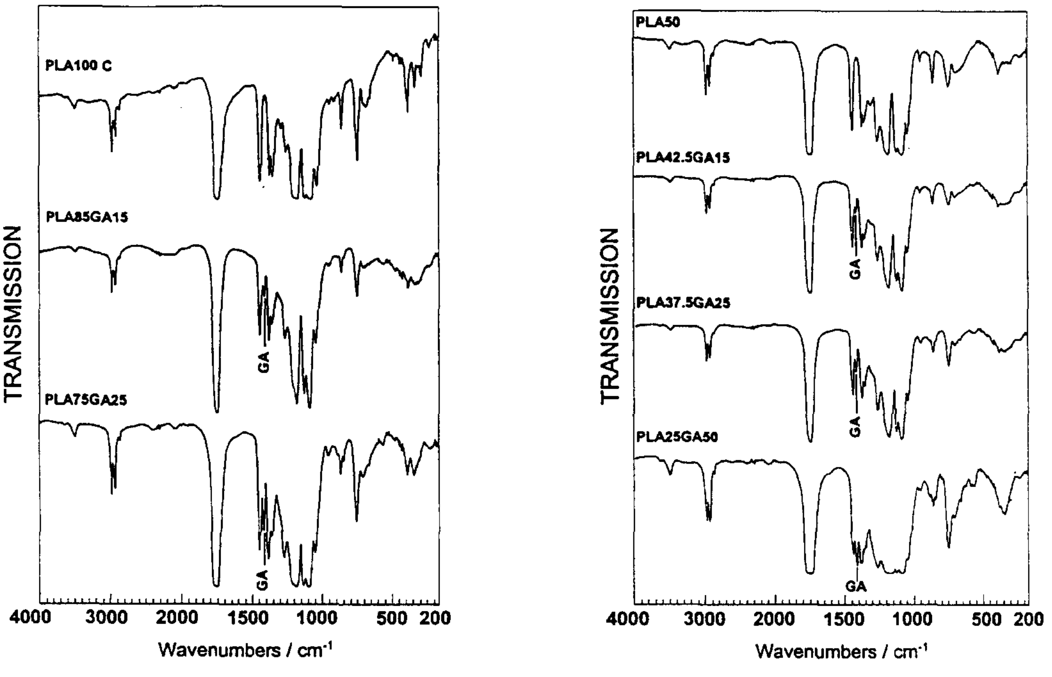

Figure 3 Infrared spectra of PLA_XGA_Y poly(lactic-*co*-glycolic)acids

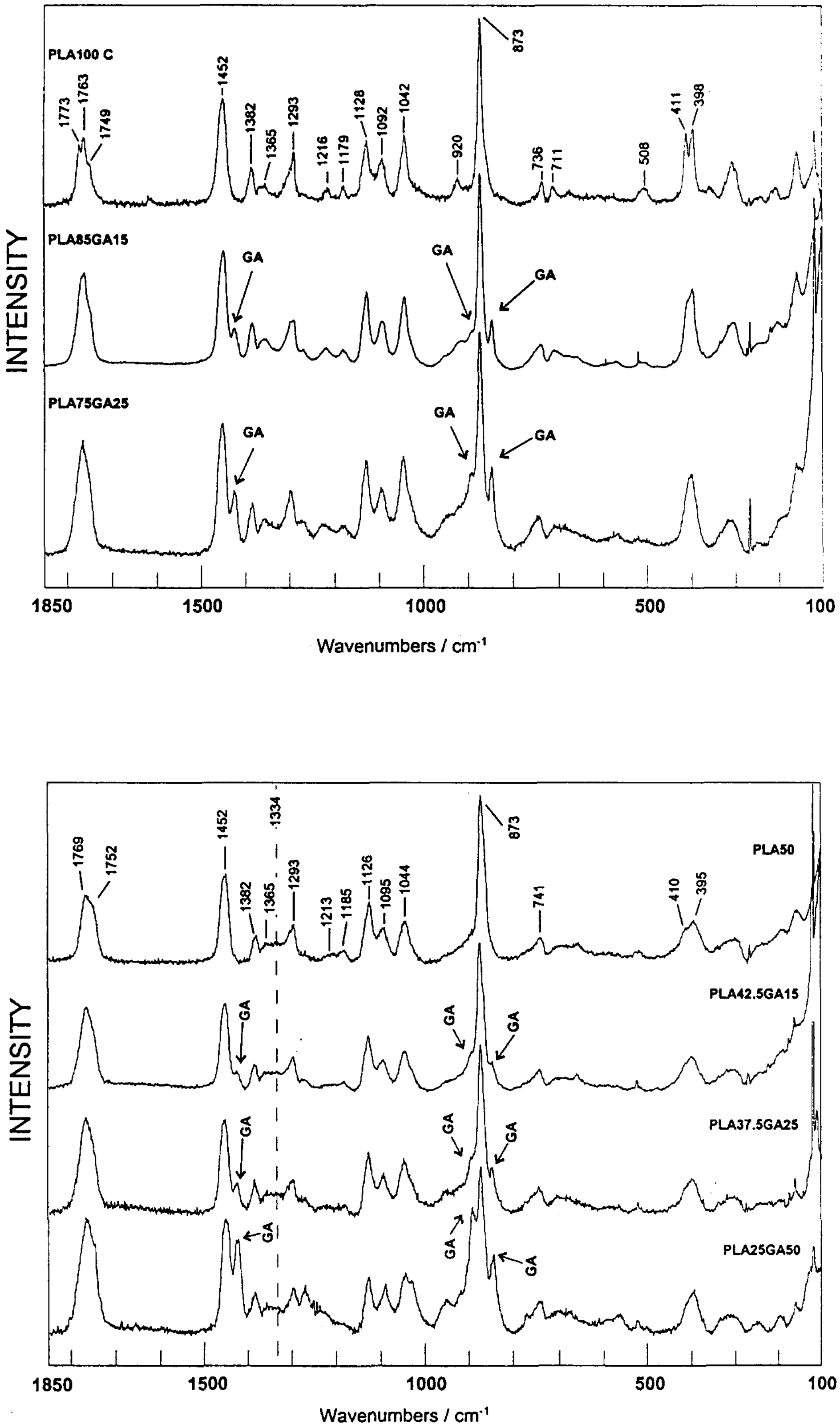

Figure 4 Raman spectra of PLA_XGA_Y poly(lactic-*co*-glycolic)acids (- - -: D-LA δCH bending vibration)

to the most intense peaks of the Raman spectrum, whereas these modes appeared as weak bands found in infra-red spectra. These modes were observed at 873 cm^{-1} in PLA_{100} and PLA_{50} and at 885 cm^{-1} in the amorphous domain of PGA[16]. The Raman spectra of PLA/GA copolymers showed a strong and sharp line at 873 cm^{-1} typical of the LA-units, and a well identified shoulder at 890 cm^{-1} due to amorphous GA-units. The intensity ratio $I_{890}/(I_{890}+I_{873})$ was calculated for the different proportions in LA and GA units. Data were quite comparable with those supplied by the

$$I_{\delta CH_2}/(I_{\delta CH_2}+I_{\delta_{as}CH_3})$$

relationship, providing a means to evaluate the monomer composition of the copolymer.

The νCOC bands of ester groups were readily identified in

Table 1 Assignment of the bands from Raman spectra

PLA			PGA		
$PLA_{100cryst}$ ν (cm^{-1})	PLA_{50} ν (cm^{-1})	Assignment	PGA_{cryst} ν (cm^{-1})	PGA_{am} ν (cm^{-1})	Assignment
1773–1769–1763–1749	1769–1752	$\nu C{=}O$	1776	1760	$\nu C{=}O$
1452	1452	$\delta_{as}CH_3$	1438	1424	δCH_2
1394–1388–1382	1382	$\delta_s CH_3$	1403	1400	wCH_2
1371–1366–1353	1365	$\delta CH + \delta_s CH_3$	1248	1274	$twCH_2$
—	1334	δCH			
1313–1302–1293	1300	δCH			
920	—	$rCH_3 + \nu CC$	998	950	$\nu CC + rCH_2$
873	873	νCC	—	885	νCC

PLA, poly(lactic acid); PGA, poly(glycolic acid)

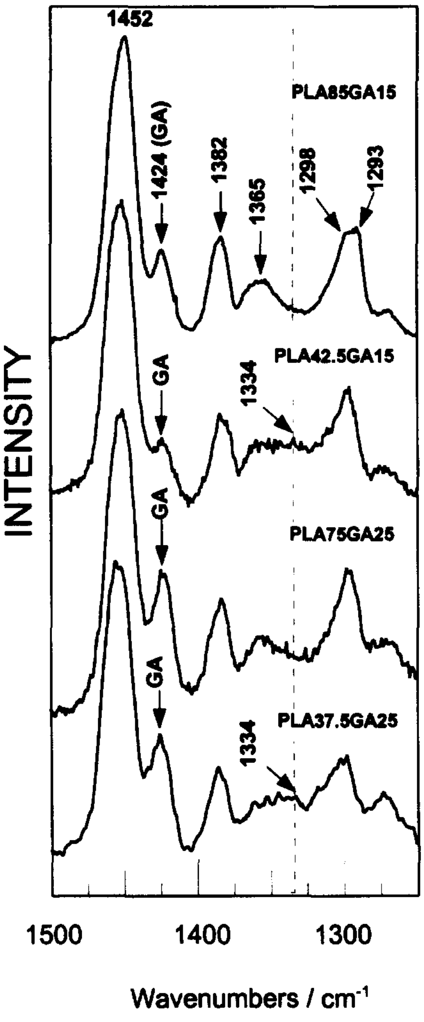

Figure 5 Raman spectra (1250–1500 cm^{-1} region) of PLA_XGA_Y poly(lactic-*co*-glycolic)acids (- - -: D-LA δCH bending vibration)

the infra-red spectra of the homopolymers. In the spectra of the copolymers (*Figure 3*), their width and overlap with other strong bands made the evaluation of the monomer composition more difficult. The Raman corresponding lines were of low intensity at about 1215–1180 cm^{-1} ($\nu_{as}COC$) and at about 1095 cm^{-1} (νCOC) for LA units and at 1268 and 1090–1028 cm^{-1} for GA units.

The carbonyl bands. These were identified at 1769 cm^{-1} ($\nu_{LA}C{=}O$) and as a shoulder at 1760 cm^{-1} ($\nu_{GA}C{=}O$) typical of LA and GA units, respectively. The differentiation of band shapes was not accurate enough to be used to determine the proportion of the monomers within the polymer chains.

Morphology

The presence of amorphous and crystalline domains in PLA_XGA_Y was investigated by comparing the Raman spectra of PLA_{100}, of semicrystalline PGA (*Figure 6*), of amorphous homopolymers (*Table 1*) and of their copolymers. PLA_{100} spectra showed split $\nu C{=}O$ stretching bands (1773–1769–1763–1749 cm^{-1}) and δCCC deformation (411 and 398 cm^{-1}) carbonyl bands corresponding to the different species of symmetry expected in the 10_3 helical conformation[19]. They also exhibited a peak at 920 cm^{-1} characteristic of the 10_3 helix[14]. In PGA Raman and infra-red spectra, the non-coincidence of some vibrational frequencies argued in favour of a plane zigzag conformation[16] presenting an inversion center in the crystalline cell[20]. The main crystalline Raman bands of PGA were found at 998 ($\nu C{-}C$ + rCH_2), 1248 ($twCH_2$) and 1776 ($\nu C{=}O$) cm^{-1}, while crystalline infra-red bands were located at 975 ($\nu C{-}C$ + rCH_2), 900 ($\nu C{-}C$), 810 ($\delta C{=}O$), 630 and 595 ($\gamma C{=}O$) cm^{-1}. None of the crystalline bands of PLA_{100} and PGA homopolymers were observed in the spectra of the $PLA_{42.5}GA_{15}$, $PLA_{37.5}GA_{25}$, $PLA_{75}GA_{25}$ and $PLA_{25}GA_{50}$, in agreement with their amorphous character. The spectra were the superposition of those of amorphous PLA_{100} and PGA for $PLA_{75}GA_{25}$, and of PLA_{50} and amorphous PGA for $PLA_{42.5}GA_{15}$, $PLA_{37.5}GA_{25}$ and $PLA_{25}GA_{50}$. In $PLA_{85}GA_{15}$, some splitting or asymmetric peaks reflected slight crystallinity (398–410 and 1293–1298 cm^{-1}). No Raman line appeared at 998 cm^{-1}, showing that GA units did not belong to long ordered sequences, but were distributed at random along the PLA/GA chain.

Configuration

The stereostructures were analysed by comparative spectra of L-LA/GA copolymers and D,L-LA/GA terpolymers in the 1300–1360 cm^{-1} region corresponding to $\delta_s CH_3$ and δCH bending modes. *Figure 5* shows that the introduction of D-lactic units in L-LA/GA chains involved the appearance of a weak, but broad Raman line at about 1334 cm^{-1} in $PLA_{42.5}GA_{15}$, $PLA_{37.5}GA_{25}$ and $PLA_{25}GA_{50}$. This new band present in the spectra of stereocopolymers of PLA_{50} (*Figure 7*) allowed

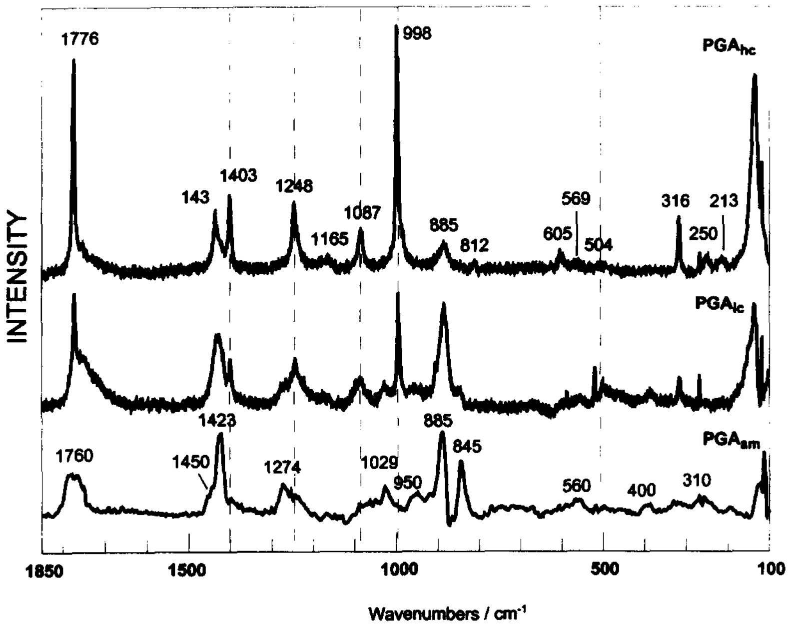

Figure 6 Raman spectra of PGA poly(glycolic acid); hc, high crystallinity; lc, low crystallinity; am, amorphous (- - -: crystalline peak)

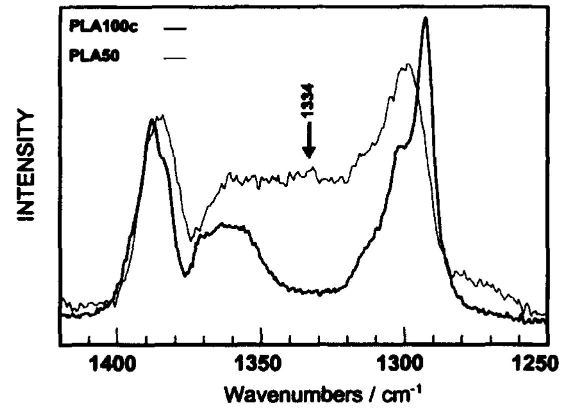

Figure 7 Raman spectra of semi-crystalline PLA_{100} and amorphous PLA_{50} in the 1250–1420 cm^{-1} region

simple differentiation of the PLA_{100} homopolymer from the stereocopolymers of the different PLA_{50} [15]. Accordingly, it allowed distinction between L-LA/GA and the D,L-LA/GA terpolymers, when ^{13}C n.m.r. spectrometry failed.

CONCLUSION

Copolymer composition, morphology and configuration of various PLA/GA lactic acid derived polymers were analysed by solid state ^{13}C n.m.r. and vibrational spectroscopy. These methods appeared suitable for the identification of PLA_XGA_Y samples directly from solid devices without any preparation. Raman spectroscopy appeared more sensitive to the stereochemistry of copolymers than CP/MAS ^{13}C n.m.r. It allowed discrimination of amorphous $PLA_{42.5}GA_{15}$ from $PLA_{85}GA_{15}$, and $PLA_{37.5}GA_{25}$ from $PLA_{75}GA_{25}$ on the basis of the appearance of a new peak at 1334 cm^{-1} in terpolymers, of frequency shifts and of the relative intensities of the δCH and $\delta_s CH_3$ bending modes corresponding to LA units. In contrast, solid state ^{13}C n.m.r. did not allow to distinguish the specific L- and D,L-LA unit distribution present in the various amorphous $PLA_{42.5}GA_{15}$ and $PLA_{85}GA_{15}$, $PLA_{37.5}GA_{25}$ and $PLA_{75}GA_{25}$ terpolymers. Solid state ^{13}C n.m.r. appeared limited in the search for information on the chemical structure of solid state PLA/GA copolymer chains.

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