PII: S0032-3861(97)00481-3

Polymer Vol. 39 No. 10, pp. 1977–1982, 1998
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0032-3861/98/$19.00+0.00

Synthesis and characterisation of copolymers of methyl acrylate and poly(glycolide) macromonomers

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(Received 23 April 1997; revised 5 June 1997)

This paper describes the synthesis of graft copolymers with a main chain of acrylic nature; the grafts attached to the backbone are composed of a biodegradable polyester, poly(glycolic acid), with well-known applications in medicine. The synthesis has been carried out by radical polymerisation of methyl acrylate and poly(glycolic acid) chains that have been functionalised previously with a methacrylic residue. These functionalised chains have been synthesised by the ring opening polymerisation of the cyclic dimer of glycolic acid, glycolide, using a functionalised initiator. All the products have been characterised spectroscopically. The thermal properties of the copolymers have also been measured. These results indicate that the copolymers have a biphasic morphology. © 1998 Elsevier Science Ltd. All rights reserved.

(Keywords: methyl acrylate; poly(glycolide); macromonomer)

INTRODUCTION

During the last two decades, polyesters derived from α-hydroxy acids such as poly(lactic acid), poly(glycolic acid) or copolyesters of both monomers, have been the most important synthetic macromolecules used for the preparation of biodegradable materials with important applications in medicine. This interest is due to a valuable set of properties, i.e. biocompatibility, non-toxicity of the degradation products and resorption after an appropriate period of implantation. These characteristics have made them potentially useful in ever increasing surgical and pharmaceutical applications [1–6]. However, the intrinsic properties of these materials are not always adequate for a specific application. For example, as matrices for controlled delivery systems, a more appropriate hydrophilic/hydrophobic balance might be desired sometimes; in their surgical applications as devices for osteotomies and the fixation of bone fractures, better mechanical properties or the maintenance of them for longer periods of time might be expected in some cases. In order to improve their mechanical properties the use of self-reinforced polyesters has been suggested. Thus, Törmälä *et al.* [7–9] have prepared fixation rods using poly(glycolic acid) or poly(L-lactic acid) reinforced with highly oriented fibres of the same polymers. These composites have good mechanical strength and can be used in the treatment of cancellous bone fractures, osteotomies, and arthrodeses instead of the classical Kirschner metallic wire fixation devices.

Another approach for the improvement of the mechanical properties of these polyesters is the use of a second biocompatible component which, in addition, would contribute to modify the hydrophilic/hydrophobic balance of the system. In this sense, the synthesis of graft copolymers containing both components, the biodegradable and the non-biodegradable one, is an interesting way of preparing composite polymers with physical and mechanical properties controlled by the average composition and sequence distribution of the comonomers along the copolymer chain as well as by the chemical structure and the length of the graft segments.

This paper deals with the preparation and characterisation of graft copolymers of poly(methyl acrylate) with grafts of poly(glycolic acid). The synthesis of these copolymers involves the previous preparation of well characterised poly(glycolic acid) oligomers functionalised with a methacrylic double bond and, in a second step, their radical copolymerisation with methyl acrylate.

EXPERIMENTAL

Preparation of glycolide

Four hundred grams of glycolic acid (Merck) are heated at atmospheric pressure under a stream of nitrogen in a round-bottom flask until the temperature of the liquid is 175–185°C. The temperature is maintained in this range until water ceases to distil (about 2 h). The pressure is then reduced over a period of 30 min to about 150 mm and the temperature maintained for an additional 2 h. The residue so obtained is poured into an enamel pan where it solidifies to a white, brittle solid. This solid is the low molecular weight poly(glycolic acid) which will be depolymerised to glycolide. One hundred grams of the powdered polyester are thoroughly mixed with 1 g of antimony trioxide and introduced in a reaction vessel equipped with a take-off for

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distilling the glycolide as it is prepared. The reaction vessel is maintained at 270–285°C at a pressure of about 5–10 mm Hg. The monomer is trapped as it is formed in a liquid nitrogen cooled two-necked flask connected to the reaction vessel. The glycolide is recrystallised twice in dry ethyl acetate with charcoal and stored in dry atmosphere.

Materials

Glycolide, prepared as described above, was recrystallised in dry ethyl acetate and dried in vacuum at 25°C for 24 h just before polymerisation. 2-Hydroxyethyl methacrylate (HEMA) was dried over molecular sieves (4A) and distilled under reduced pressure just before use. Triethylaluminium, 1 M solution in hexane (Aldrich) was used as received. Methyl acrylate (Aldrich) was washed with a solution of NaOH, 5%, then with cool water, dried with $CaCl_2$ and distilled under reduced pressure. Dichloroethane was refluxed over P_2O_5 and distilled just before use. Dioxane was repeatedly refluxed over KOH, filtered and dried with Na, and distilled before use. DMSO was first dried with KOH and then with CaH_2; it was fractionally distilled at low pressure just before use.

Synthesis of poly(glycolic acid) (PGA) macromonomer

Twenty millilitres of dichloromethane and 1 ml of triethylaluminium solution were placed in a flask which had been carefully flamed and purged with nitrogen, and equipped with a rubber septum. Under vigorous stirring, 1 mmol of strictly anhydrous and freshly distilled HEMA in 5 ml of dichloromethane was slowly added to the flask at 0°C. The catalyst solution was kept under stirring for an extra 1 h at room temperature and 30 min at 40°C. Then, a solution of glycolide (10 mmol in 30 ml of dichloromethane) was added. The reaction mixture was kept at 25°C for 20 h. After this time, trifluoroacetic acid was slowly added until most of the macromonomer was dissolved. The solution was filtered and the macromonomer was isolated by precipitation in diethyl ether.

Radical copolymerisation of PGA macromonomer with methyl acrylate (MA)

Copolymerisations were carried out in DMSO at 80°C, under nitrogen atmosphere and using benzoyl peroxide (BP) as initiator ($[BP] = 1.5 \times 10^{-2}\ mol\ l^{-1}$). Three different MA/macromonomer (w/w) compositions were formulated: 1/1, 2/1 and 4/1, the monomer concentration being in all cases $[MA] = 1\ mol\ l^{-1}$. The reaction time was 20 h. The copolymers were isolated by precipitating the reaction mixtures in methanol. Conversion higher than 90% wt was obtained.

Measurements

^1H and ^{13}C n.m.r. spectra were recorded in deuterated chloroform/trifluoroacetic mixture solution with a Varian VXR-300 spectrometer. The samples were thermally characterised by differential scanning calorimetry (d.s.c.) (Perkin–Elmer DSC-2C) at a scan rate of 20°C min^{-1}.

RESULTS AND DISCUSSION

Synthesis of poly(glycolic acid) (PGA) macromonomers

Since Milkovich [10] pioneered in the 1970s the widespread use of macromonomers for synthesising well defined graft copolymers, the so-called 'macromonomer technique' has become the most effective method to produce these copolymers. This method offers a better control of the number of grafts and their length than procedures involving 'grafting onto' or 'grafting from'.

Macromonomers are linear polymeric or oligomeric species which, because of the presence of a reactive end group, commonly a double bond, have the potential to polymerise with other comonomers. They can be synthesised by either initiating a living polymer or terminating it with an organic compound that bears the required double bond [11].

In order to obtain macromonomers of several polylactones with controlled chemical structure and molecular weight, Jérome and Teyssié [12–15] suggested the use of initiators based on aluminium alkoxides bearing functional groups that could be active in a further polymerisation process. As shown in *Figure 1*, the functional group R associated with the alkoxy residues of the initiator is, after polymerisation, selectively attached to the polyester chain end, whereas the other end is always a hydroxyl group, which results from the hydrolysis of the active growing centre. Thus, these authors prepared interesting poly(ε-caprolactone) and poly(δ-valerolactone) macromonomers with allylic, methacrylic, amino and bromine end-groups.

Following the ideas suggested by Jérome and Teyssié, we studied the synthesis of poly(L-lactide) macromonomers using aluminium trialkoxides bearing oxyethylmethacrylate units [16]. The ring-opening polymerisation of L-lactide initiated by this catalyst proceeds without cyclisation under controlled reaction conditions, giving rise to the formation of linear polyester chains with controlled molecular weight and structure of the functional end-groups. This polymerisation follows a 'coordination-insertion' mechanism that involves the selective rupture of the acyl–oxygen bond of the monomer and the insertion into the alkoxide–aluminium bond of the initiator.

The successful synthesis of the poly(L-lactide) macromonomers led us to extend this polymerisation procedure to the ring opening polymerisation of glycolide. As described in the experimental part, the reaction was carried out in a similar manner to that with the L-lactide. In this case, however, a monoalkoxide was used as initiator instead of the trialkoxide, and solvents of higher polarity than toluene were also selected. The reason of this change in solvent polarity is as follows: high molecular weight poly(glycolide) is known to be very insoluble in common organic

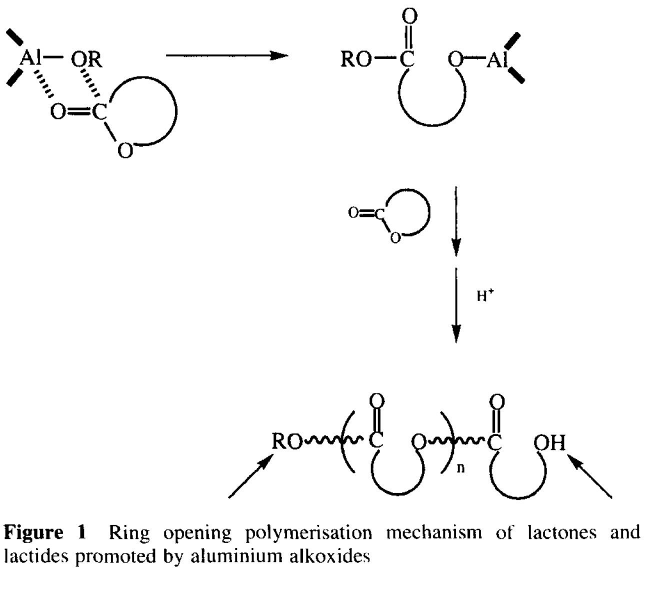

Figure 1 Ring opening polymerisation mechanism of lactones and lactides promoted by aluminium alkoxides

solvents; in fact, it has only been described to be soluble in boiling nitrobenzene or nitromethane, hexafluoro-2-propanol and mixtures of chloroform and trifluoroacetic acid. Owing to the higher solubility of low molecular weight polymers (oligomers) compared with high molecular weight species, we chose three polymerisation solvents with increasing polarity in order to find one in which the reaction medium could be homogeneous, but low enough for the polymerisation to be expected to progress. These solvents were 1,4-dioxane, dichloromethane and dimethylsulfoxide. It was found that the polymerisation succeeded in the first two solvents but failed when it was carried out in dimethylsulfoxide.

The coordination-insertion mechanism of the ring-opening polymerisation of lactones and lactides [17] requires the coordination of the monomer with the aluminium ligand as a first step before the selective rupture of the acyl–oxygen bond of the glycolide ring. The presence of polar substances in the reaction medium has been proved to affect this process as they compete with the monomer for the coordination with the aluminium ligand [17,18]. As a result, the polymerisation rate decreases with the increase of the polar character of the solvent. Dimethylsulfoxide probably lies on this category of solvents and the strong interactions with the initiator are likely to make the polymerisation rate at 25°C extremely low, or even prevent it. Similar results are obtained when it is tried to polymerise glycolide through an anionic mechanism in the same solvent [19].

As already mentioned, polymerisation took place when dichloromethane or dioxane were used as solvents. However, it must be pointed out that in both cases the macromonomer began to precipitate after 2 h of reaction.

Figure 2A shows the ^{1}H n.m.r. spectrum of the isolated product dissolved in a $CDCl_3/F_3CCOOD$ mixture. Along with the signal at 4.98 ppm, corresponding to the methylene group of the polyglycolide chain, a number of weak signals can also be distinguished which correspond to the macromonomer chain ends. In order to identify the chemical nature of the end-groups, this spectrum was compared with those of low molecular weight compounds that could reproduce these chain ends, i.e. 2-acetoxyethyl methacrylate and methyl glycolate, whose ^{1}H n.m.r. spectra are shown in *Figure* 2B and *Figure* 2C, respectively. As can be seen, there is a good agreement between the signals of the methacrylic double bond, including the α-methyl group of the macromonomer (*Figure* 2A), and those of the model compound 2-acetoxyethyl methacrylate (*Figure* 2B). However, there are slight differences related mainly to the multiplicity and chemical shift of the oxyethylene group in the methacrylate unit, as well as the methylene group directly attached to the hydroxyl end-group. If we analyse the ^{1}H n.m.r. spectra of the model compounds, we can see that the chemical shifts of these structures are around 4.47 ppm and very close one to each other; in fact there is only a difference of 0.05 ppm. In addition, both appear as

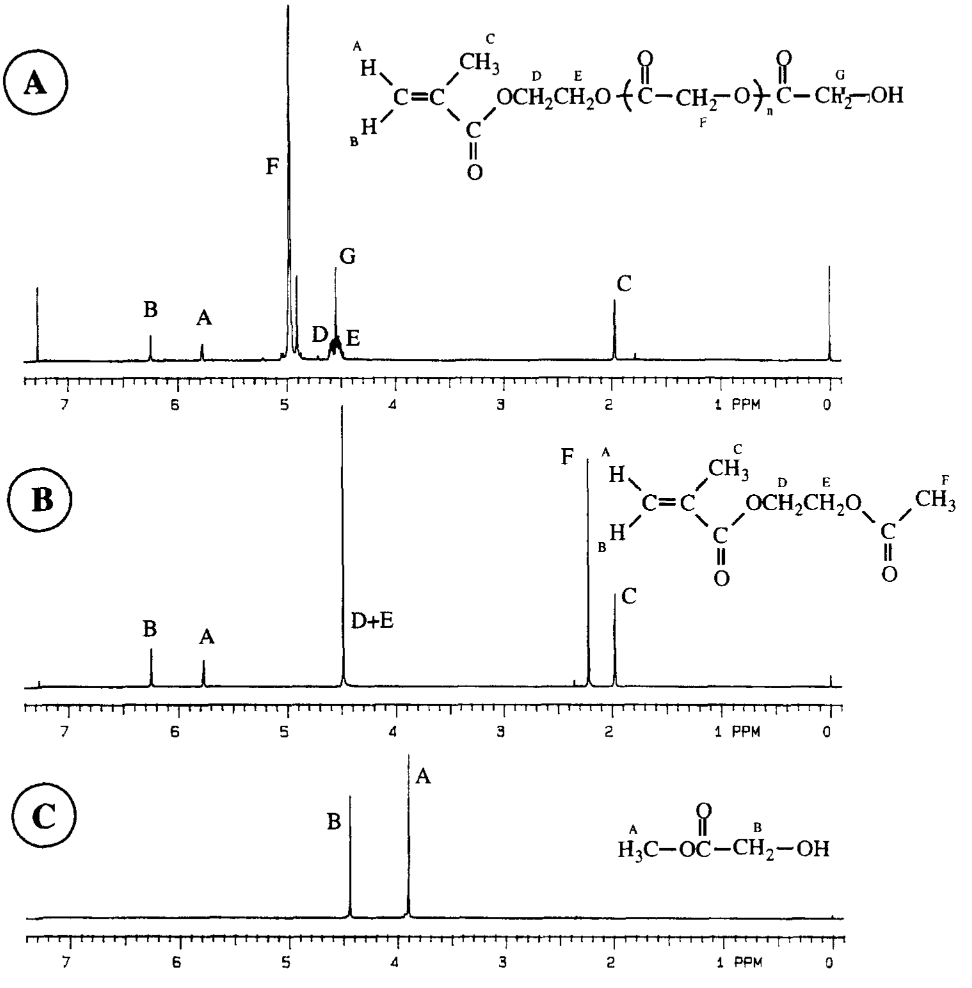

Figure 2 ^{1}H n.m.r. spectra of PGA macromonomer and chain-end model compounds: (A) PGA macromonomer; (B) 2-acetoxyethyl methacrylate; (C) methyl glycolate

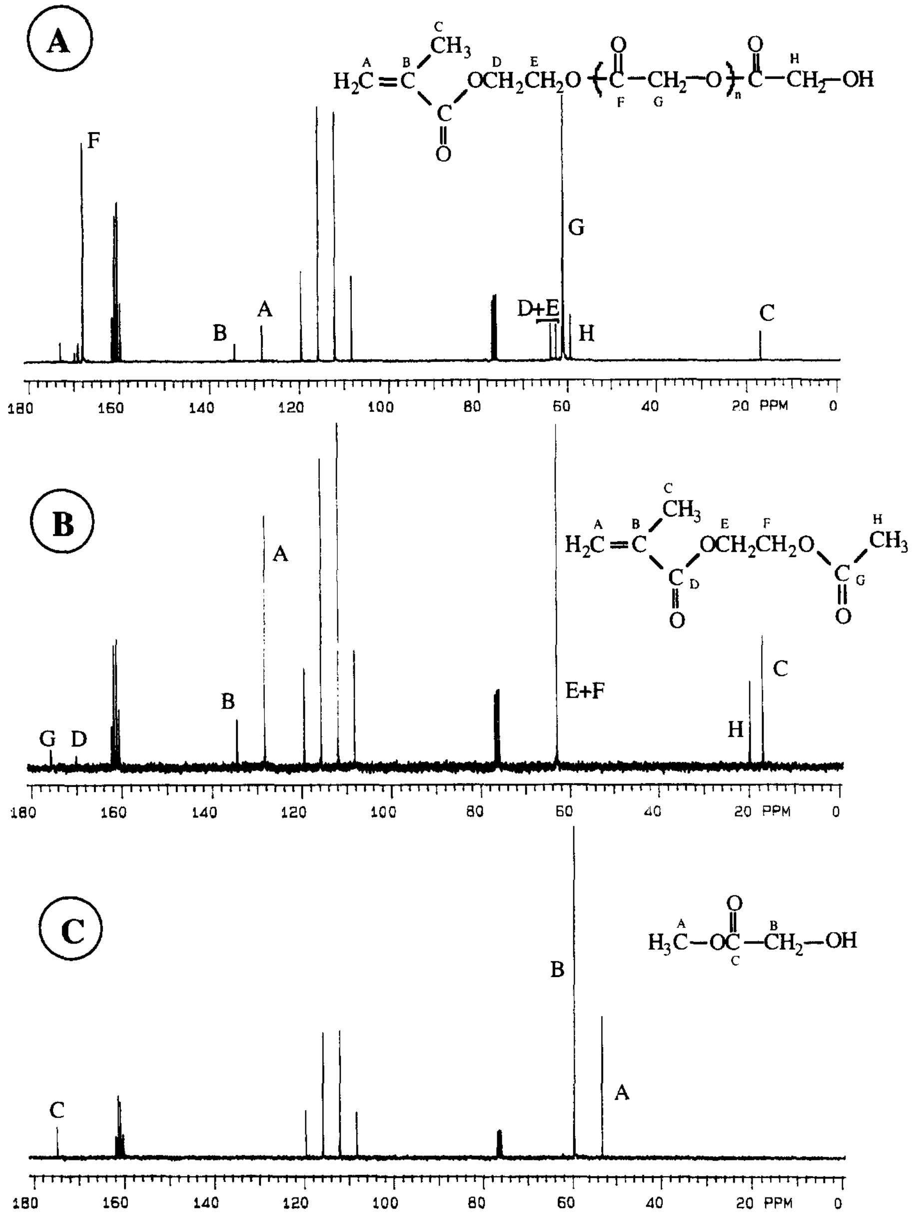

Figure 3 ^{13}C n.m.r. spectra of PGA macromonomer and chain-end model compounds: (A) PGA macromonomer; (B) 2-acetoxyethyl methacrylate; (C) methyl glycolate

singlets. Nevertheless, in the macromonomer spectrum, we observe, between 4.50 and 4.65 ppm, a sharp singlet and two additional complex multiplets. Presumably, the first one should correspond to the methylene group at the end of the chain and the other two signals to the oxyethylene in the methacrylic unit. In order to clarify this, we also analysed the ^{13}C n.m.r. spectra of the same products, which are shown in *Figure 3*. In this case, there is a clear difference in the chemical shifts of the groups that are being discussed: the methylene in the glycolate appears at 59.49 ppm and, the two oxyethylene carbons in the methacrylate, which are not magnetically equivalent, at 62.92 and 62.97 ppm. When the ^{13}C n.m.r. spectrum of the macromonomer is considered, a signal at 59.3 ppm can be distinguished, which corresponds to the methylene unit attached to the hydroxyl end-group, and another two signals at 62.56 and 63.70 ppm, corresponding to the carbons of the oxyethylene group in the methacrylic unit. It must be stressed that the higher difference between these two last signals (0.14 ppm) compared with the model compound (0.05 ppm), must be related to the fact that the protons of this unit seem to be

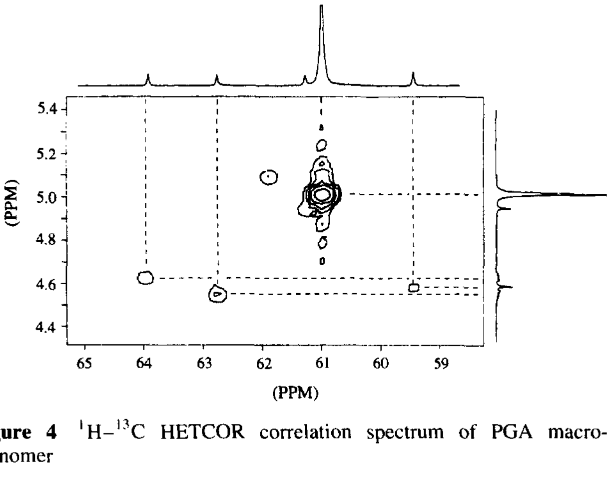

Figure 4 ^{1}H–^{13}C HETCOR correlation spectrum of PGA macromonomer

Table 1 Solubility behaviour of the different compositions of copolymer MA/PGA

	$CHCl_3$	THF	Dioxane	DMF	DMSO
Cop. A	− *	− *	− *	+	+
Cop. B	− *	− *	− *	+	+
Cop. C	− *	− *	− *	+	+
Macro.	−	−	−	−	+ **

+ , soluble; − , insoluble; *, swelling; **, soluble at $T > 80°C$.

Table 2 Copolymer composition

	MA/-CH_2-CO-O- molar ratio in the feed	MA/-CH_2-CO-O- molar ratio in the copolymer
Cop. A	0.67	0.79
Cop. B	1.34	1.46
Cop. C	2.69	2.91

magnetically equivalent in the model compound but not in the macromonomer.

To confirm the relationship between the ^1H and ^{13}C spectra we also used a $^1H-^{13}C$ HETCOR correlation experiment of the macromonomer, which is shown in *Figure 4*. As can be seen, there is a good agreement with the assignments made before which confirms the chemical nature of the end-groups of the macromonomer.

In order to characterise the molecular weight of the macromonomer the area of the ^1H n.m.r. spectrum of the methacrylic protons was compared with that of the methylene group of the polyester chain. Thus, the molecular weight obtained was $M_n = 1300$. As the macromonomer precipitates when a critical molecular weight is reached, this value can be considered as the maximum molecular weight attainable under the polymerisation conditions used. In this sense, Jérome *et al.* [20] have recently proposed the use of ω-Al-alkoxide poly(ε-caprolactone) macroinitiators for the ring opening polymerisation of glycolide. They obtain stable colloidal dispersions of block copolymers caprolactone/glycolide with polyglycolide segments longer than those attained using HEMA-functionalised alkoxides.

Finally, solubility tests showed that the macromonomer was insoluble in chloroform, THF, dioxane or DMF, but it was soluble in chloroform/trifluoroacetic acid mixtures, hexafluoroisopropanol or in DMSO at 80°C.

Radical copolymerisation of the PGA macromonomer with methyl acrylate (MA)

Copolymerisation reactions were carried out in DMSO at 80°C using benzoyl peroxide as initiator and three different macromonomer/methyl acrylate molar compositions. After the copolymers were purified, solubility tests were employed in order to verify the complete incorporation of the macromonomer into the copolymer. As shown by the results collected in *Table 1*, clear solutions were obtained in DMF whatever the composition of the copolymers. Taking into account that the macromonomer was insoluble in DMF, those results mean that most of the macromonomer has been incorporated into the copolymer. Finally, the copolymer compositions were calculated by means of the corresponding ^1H n.m.r. spectra and the results are summarised in *Table 2*. As an example, *Figure 5* shows the ^1H n.m.r. spectrum of one of the copolymers: signals at 4.98 ppm (methylene group of the polyglycolide chain) and 3.75 ppm (methyl group of the methyl acrylate unit) were used to calculate the copolymer composition.

Their thermal behaviour was also studied by d.s.c. The results obtained are summarised in *Table 3*. The T_g data show an increasing stiffness of the copolymer main chain with the macromonomer content. This can be readily understood if we take into account that the macromonomer chains in the copolymer are able to crystallise: although only the T_m value for the copolymer with the highest macromonomer content is given, there is evidence that crystallisation takes place even in the copolymer with the lowest macromonomer content. The incompatibility between polyglycolide and polyacrylate segments as well as the high crystallisation tendency of polyglycolide favour the reorganisation of these chains to form separate domains with high degree of crystallinity. These microdomains can act as physical crosslinking agents which lead to an increase

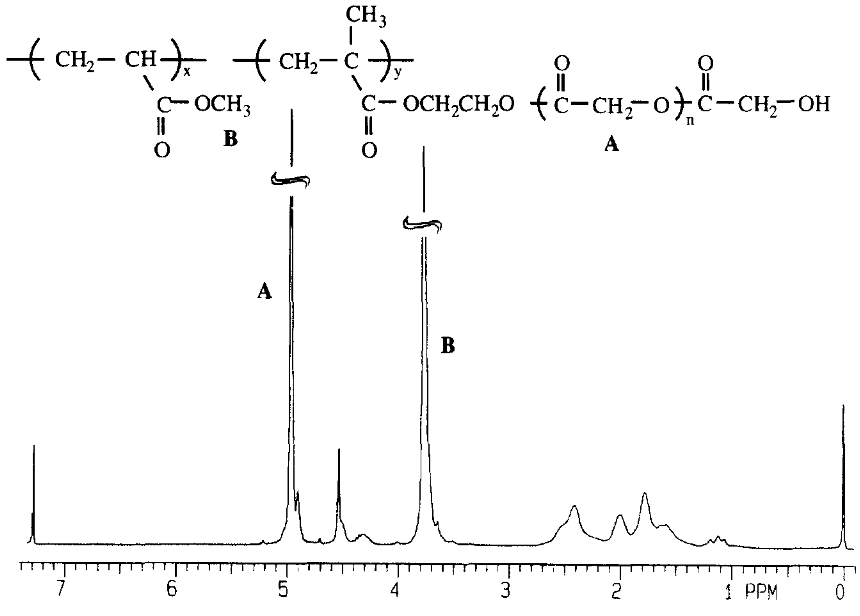

Figure 5 ^1H n.m.r. spectrum of poly(MA-co-PGA macromonomer)

Table 3 Thermal properties of the different systems

	T_g (°C)	T_m (°C)
Macromonomer	10	171
Copolymer A	23	161
Copolymer B	22	–
Copolymer C	15	–
Poly(methyl acrylate)	10	–

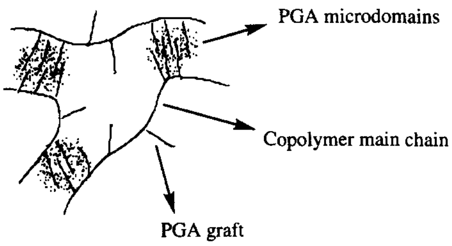

Figure 6 Schematic microphase separation in graft copolymers. Presence of PGA semicrystalline microdomains

in the stiffness of the main chain. *Figure 6* represents the possible copolymer morphology arising from the formation of crystalline microdomains.

We have also observed this phenomenon in several copolymers containing polylactide macromonomers [21]. As materials with biomedical applications, it must be stressed that the presence of these microdomains determines their behaviour in hydrated media. As an example, we have seen that in copolymers of vinyl pyrrolidone or *N,N'*-dimethylacrylamide with semicrystalline or amorphous polylactide macromonomers, the swelling behaviour strongly depends on the existence of such domains but particularly on their semicrystalline or amorphous nature. Thus, the swelling degree of amorphous samples is at least twice that of crystalline ones. This study, which will be the subject of a forthcoming paper, has also revealed the influence of the morphology, not only on the degree of swelling but also on the kinetic aspects of the swelling process.

ACKNOWLEDGEMENTS

Financial support from the Departamento de Economía of the Diputación Foral de Gipuzkoa and DGICYT (Project n. PB 94-0463) is gratefully acknowledged.

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