International Journal of Pharmaceutics, 70 (1991) 77–85
© 1991 Elsevier Science Publishers B.V. 0378-5173/91/$03.50
ADONIS 037851739100161T

IJP 02349

Biodegradable controlled release tablets

1: Preparative variables affecting the properties of poly(lactide-co-glycolide) copolymers as matrix forming material

K. Avgoustakis and J.R. Nixon

King's College London, Chelsea Department of Pharmacy, University of London, Manresa Road, London SW3 6LX (U.K.)

(Received 15 October 1990)
(Accepted 21 November 1990)

Key words: Poly(lactide-co-glycolide) copolymer; Preparative variables; Biodegradable implanted tablet

Summary

A detailed study of the synthesis of poly(lactide-co-glycolide) copolymers for use as biodegradable polymers in the preparation of controlled release implantable matrix tablets has been undertaken. The factors examined were the catalyst (type and concentration), co-catalyst concentration and time and temperature of polymerization. The samples were examined for their molecular weight by viscometry, composition by ^{1}H-NMR spectroscopy, microstructure by ^{13}C-NMR spectroscopy and morphology by differential scanning calorimetry. The percentage yield and the reproducibility of polymerization were also investigated. Comparison of two widely used catalysts — antimony trifluoride and stannous octoate — revealed that stannous octoate was far more effective and this catalyst was investigated further. At both low and high levels of temperature, with increasing the catalyst level there was an initial sharp increase in the molecular weight but this passed through a maximum before falling at higher catalyst levels. The effective catalyst concentrations depend on the temperature of polymerization and higher molecular weight polymers were obtained at the lower temperature. Temperatures in excess of 190°C caused polymer decomposition. The high molecular weight polymers were hard, but not brittle, "elastic" materials which might limit their application in tableting. The percentage yield is less affected by the temperature than by the catalyst level. The change in percentage yield with respect to the catalyst level followed the same pattern as the change in molecular weight. Increased levels of co-catalyst (lauryl alcohol) caused both a lowering of molecular weight and percentage yield. At both levels of temperature the molecular weight and percentage yield increased up to 4 h reaction time, but the molecular weight fell at longer reaction times whilst the percentage yield remained essentially constant. The composition of the samples was affected by the polymerization time. However, the composition did not change at reaction times longer than 4 h. From these results it appears that 4 h is the optimum polymerization time. All samples produced have been shown to be block copolymers which were amorphous and whose glass transition temperatures depended on composition and molecular weight. Glass transition temperatures as low as 37°C were measured which could have a significant effect on drug release, when formulated as implanted tablets.

Introduction

Biodegradable polymers have become increasingly important in the development of controlled

---

Correspondence: J.R. Nixon, King's College London, Chelsea Dept. of Pharmacy, University of London, Manresa Rd, London SW3 6LX, U.K.

release drug delivery systems. A number of biodegradable polymers have been developed and evaluated for delivery of drugs, but the polymers achieving the most success at this time are these prepared from lactic and glycolic acids. These polymers combine a number of desirable properties, the most important being that their degradation rate can be controlled over a wide range by changing their composition. So far the predominant application of poly(lactide-co-glycolide) copolymers has been subcutaneous injectable systems in the form of suspended powders (microcapsules), thin rods, or small beads (Kitchell and Wise, 1985).

This work concerns the preparation and evaluation of matrix tablets using poly(lactide-co-glycolide) as the matrix forming material. These tablets are intended for subcutaneous implantation and the drug release will be controlled by the properties of the polymer and the formulation process.

Commercially, poly(lactide-co-glycolide) copolymers are not available yet in an adequate range or with adequate characterization. This is mainly because the preparation process affects their chemical, physical and mechanical properties in a way that is not well understood and prevents the preparation of products with consistent properties. This probably accounts for the contradictory findings for the biodegradation behaviour of these polymers reported in the literature (Wise et al., 1979).

In the first part of this work a detailed study of the synthesis of these polymers has been attempted. The effect of several preparative variables on properties of the polymer such as molecular weight and composition, and on the yield of the polymerization has been investigated. The microstructure of the resulting polymers, which has been reported to affect their degradation rate (Chabot et al., 1983; Dunn et al., 1988), has also been considered.

Materials and Methods

Materials

The following chemicals were used: dl-lactic acid (Aldrich), glycolic acid (Aldrich), stannous octoate (Sigma), antimony trifluoride (Aldrich), antimony trioxide (Aldrich), lauryl alcohol (BDH), tetrahydrofuran (FSA), chloroform (FSA), ethyl acetate (FSA) and acetone (FSA).

Methods

Synthesis of polymers The synthesis of poly (lactide-co-glycolide) copolymers was based on the method described by Gilding and Reed (1979): 600 g of 80% dl-lactic acid solution in water and 1.44 g of Sb_2O_3 were put in a 1000 ml round-bottom flask fitted with a distillation head and condenser. The vessel was heated in a silicone oil bath at 140°C while the contents were stirred using a magnetic stirrer. When the rate of water elimination fell a water aspirator was connected to the apparatus and the temperature was increased gradually to 180°C. After no further water was evolved an air condenser substituted for the water type and an oil pump for the water aspirator and a clean receiver cooled in liquid nitrogen was attached. The temperature was then raised to 250°C and the vacuum increased to 0.1–0.5 mmHg. Lactide sublimed and distilled over as a pale yellow waxy solid. The yellow colour was removed by washing with chloroform and after two recrystallizations from ethyl acetate and one from acetone, a shiny white crystalline material was obtained with a melting point of 124°C.

Glycolide was prepared following the same procedure. The purified white crystalline material had a melting point of 82°C.

The polymerization mixtures were put into thick-walled glass tubes which were then evacuated, after prior flushing with nitrogen, sealed and heated in an oven for the specified period of time.

The resulting glassy colourless to green solids were dissolved in tetrahydrofuran to make approx. 20% w/v solutions. These solutions were precipitated in excess distilled water and the polymers were collected as white cocoons on glass rods. The purified polymers were dried in a vacuum oven at 40°C for 48 h.

The synthesis variables studied were the catalyst type and concentration, the co-catalyst (lauryl alcohol) concentration and the time and temperature of polymerization.

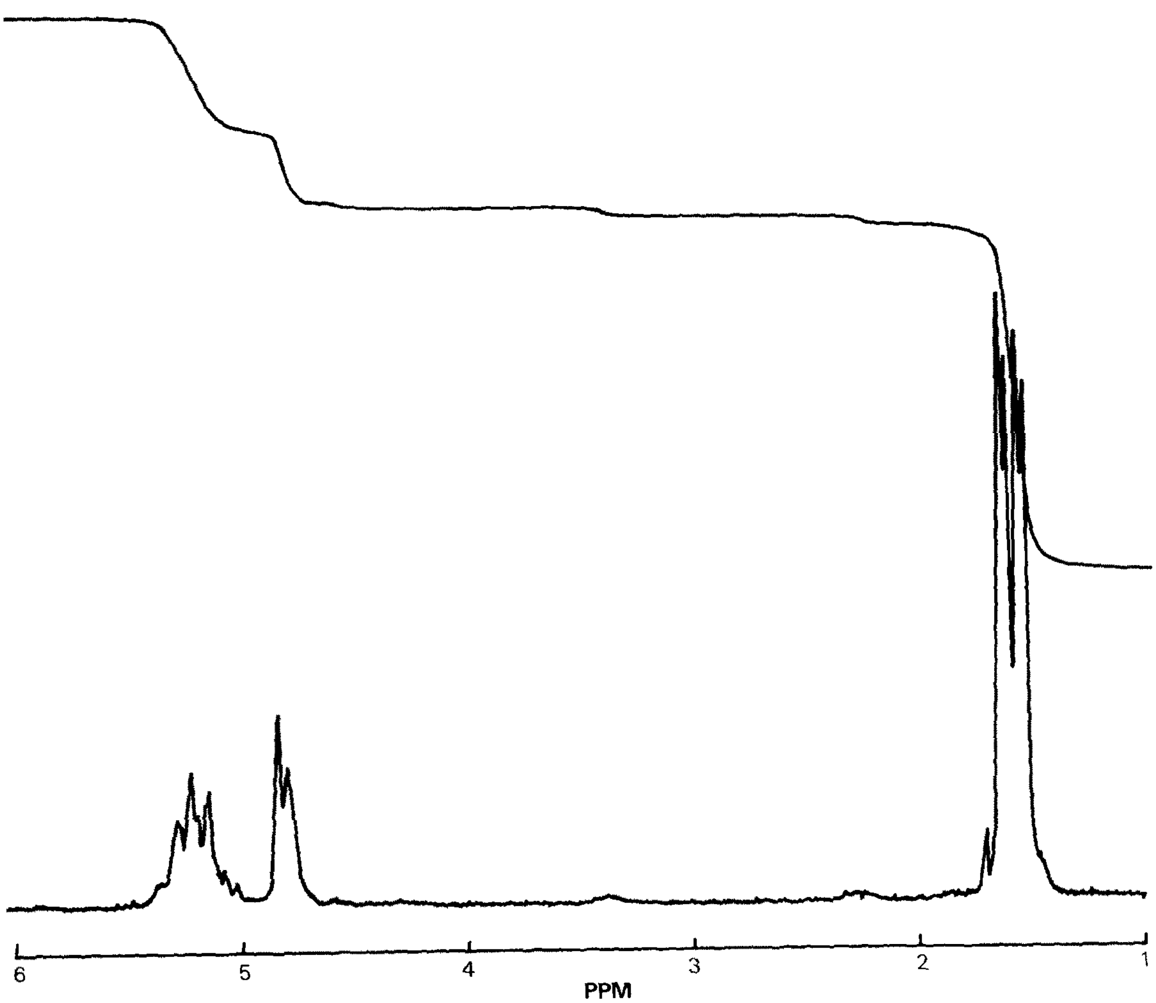
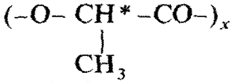


Fig. 1. ^{1}H-NMR spectrum of an 80 : 20 (initial lactide : glycolide w/w ratio) copolymer in $CDCl_3$.

Characterization of polymers The identity and purity of the polymers was investigated by IR and ^{1}H-NMR spectroscopy. The IR spectra were determined in a SP-800 spectrophotometer over the range 4000–600 cm^{-1}. KBr discs, containing approx. 1% w/w of the compound being examined, were used with air as reference.

The ^{1}H-NMR spectra were recorded with a Perkin Elmer R32 spectrometer operating at 90 MHz. The polymers were dissolved in $CDCl_3$ and TMS was used as internal standard. The composition of the samples was determined by comparing the integrals of the surface of the peaks assigned to the lactic backbone proton:



$(-O-\underset{\underset{CH_3}{|}}{CH^*}-CO-)_x$

and to the glycolic protons $(-O-CH_2^*-CO-)_y$ (Fig. 1). The microstructure of certain samples was also examined using ^{13}C-NMR spectra, recorded in a Bruker WM250 spectrometer operating at 62.8 MHz. The polymers to be examined were dissolved in DMSO and TMS was used as internal standard.

Differential scanning calorimetry (DSC) was used to study the effect of the preparative variables on the morphology of the polymers. The thermograms were obtained with a Du Pont 910 instrument coupled with a Du Pont 9000 analyser at a heating rate of 10°C/min. Two runs were made with each sample, the first serving as a technique to provide a standard thermal history for all samples.

The molecular weight of the samples was determined by viscometry. The flow time of 1% solutions of the samples in chloroform was measured using an Ubbelohde suspended level viscometer (size A) and the inherent viscosity (iv) was calculated.

Results and Discussion

The study of factors affecting the synthesis of poly(lactide-co-glycolide) was conducted using two different proportions of monomer mixture, namely 90 : 10 and 70 : 30 lactide : glycolide (w/w). Because the composition of the resulting polymers is not constant, being dependent on the polymerization conditions, the copolymers produced in this work are normally referred to by the initial lactide : glycolide ratio from which they were produced.

During preliminary experiments the recrystallization process was found to significantly affect the polymerization. When the crystallization was induced by an ice-water bath, small crystals of lactide and glycolide were obtained. These crystals did not give reproducible polymerization behaviour and resulted in low molecular weight polymers. However, when crystallization was allowed to occur slowly at ambient temperature, large crystals of lactide and glycolide were obtained which gave reproducible polymerization and resulted in high molecular weight polymers. This phenomenon could be attributed to the difference in specific surface area between large and small crystals. These cyclic diesters are sensitive to traces of atmospheric moisture, being converted during storage to acidic oligomers which cause erratic polymerization behavior. The small crystals, having larger specific surface area, will be more labile to moisture. Moreover when the crystallization of glycolide proceeds at a low temperature, the form which is more sensitive to moisture is produced (Frazza and Schmitt, 1971).

A typical IR spectrum of a 77 : 23 lactic : glycolic acid copolymer is shown in Fig. 2. The major peaks assigned to the structure of poly(lactide-glycolide) copolymers are: 3500 cm^{-1} (O–H stretching), 2950 and 3000 cm^{-1} (C–H stretching), 1750 cm^{-1} (ester C=O stretching), 1450 cm^{-1} (C–H bending) and 1100 cm^{-1} (C–O stretching). The IR and ^{1}H-NMR spectra show that the copolymers produced are pure and genuine (Figs 1 and 2).

Lewis acids and organometallic compounds are two types of catalyst that have been reported to be particularly effective in the ring opening polymerization of lactide and glycolide. Antimony trifluoride is a widely used representative of the first

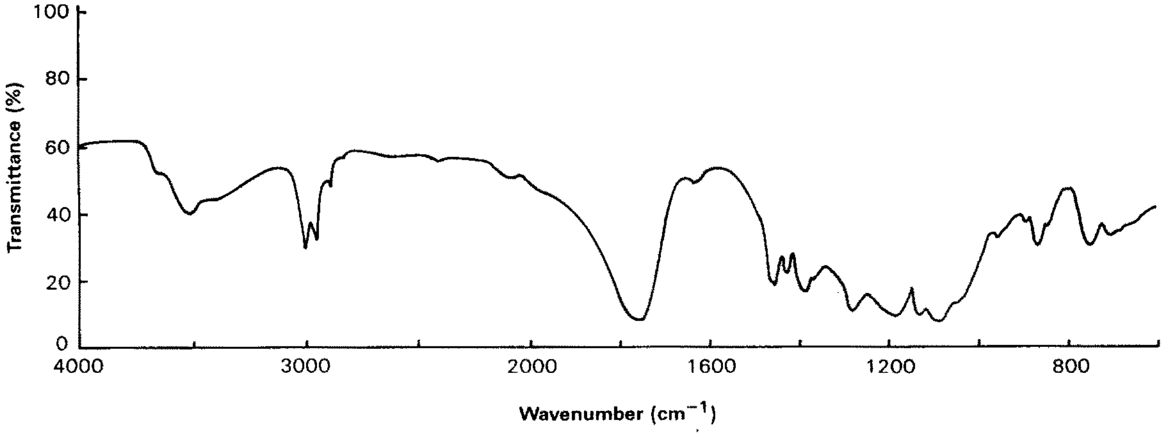


Fig. 2. IR spectrum of a 77 : 23 poly(lactide-co-glycolide) copolymer.

TABLE 1

Effect of type of catalyst on the inherent viscosity (dl/g) of the copolymers

Reaction conditions [a]	Stannous octoate		Antimony trifluoride	
	90:10 [b]	70:30	90:10	70:30
0.03% catalyst, 190°C	0.698	0.593	0.185	0.191
0.1% catalyst, 130°C	0.805	0.640	0.090	0.141

[a] 4 h polymerization.

[b] Initial lactide : glycolide w/w ratio.

category and stannous octoate of the second (Lowe, 1954; Chujo et al., 1967; Gilding and Reed, 1979; Deasy et al., 1989). The results obtained when using these catalysts are given in Table 1. Under both polymerization conditions stannous octoate was far more effective and this catalyst was chosen for the remainder of this work.

The polymerization of lactide and glycolide has been reported to be cationic (Frazza and Schmitt, 1971). This type of polymerization often proceeds at a very high rate which increases the difficulty of obtaining reproducible results (Billmeyer, 1984). Our reproducibility of polymerization has been checked by producing two batches of 90:10 copolymer under identical conditions (0.03% w/w catalyst, 190°C for 1 h). The results obtained ($iv_1 = 0.459$, $yield_1 = 56.0\%$ and $iv_2 = 0.500$, $yield_2 = 46.3\%$) were regarded as showing a satisfactory reproducibility.

The effect of catalyst concentration on the polymer molecular weight under two reaction temperatures is shown in Figs 3 and 4. At both temperatures there was an initial sharp increase in the molecular weight at low catalyst levels, but this passed through a maximum before falling at higher levels of catalyst. It appears that higher molecular weight polymers were obtained at the lower temperature level (130°C). The results also show that the effective catalyst concentrations depend on the temperature at which the polymerization proceeds. Temperatures in excess of 190°C have been observed to cause polymer decomposition, when a 4 h polymerization time was used, giving a brown colour to the products. Polymers with inherent viscosity of less than 0.3, which were prepared using very low catalyst levels, are yellowish brittle materials that can be easily powdered by grinding. Polymers with inherent viscosity more than 0.3 are hard but not brittle, 'elastic' materials that cannot be powdered by grinding. It would thus appear that the physical nature of the high molecular weight polymers might limit their applicability in the manufacture of matrix tablets.

The effect of catalyst concentration on the percentage yield of the reaction is shown in Table 2. It appears that the yield is less affected by the reaction temperature than by the catalyst level. The change in yield with respect to the catalyst level followed the same pattern as the change in molecular weight. There is thus a sharp initial increase of the yield but this reaches a maximum

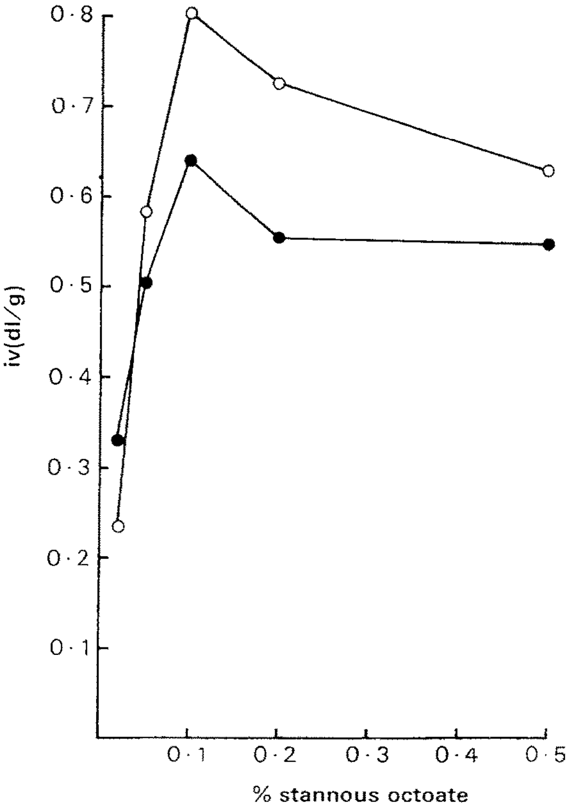


Fig. 3. Effect of catalyst concentration on polymer molecular weight (polymerization at 130°C for 4 h). Initial lactide : glycolide ratio (w/w): (○) 90:10, (●) 70:30.

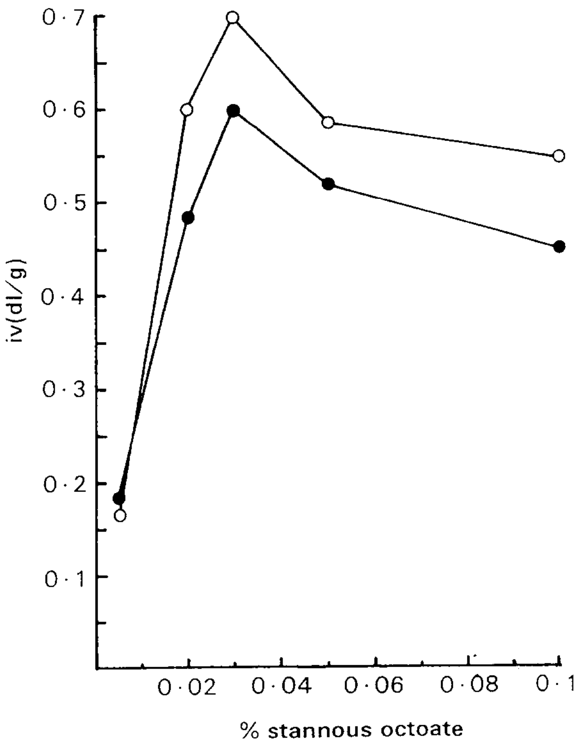


Fig. 4. Effect of catalyst concentration on polymer molecular weight (polymerization at 190°C for 4 h). Symbols as in Fig. 3.

at the effective catalyst levels before falling at higher catalyst levels.

Dittrich and Schultz (1971) reported that the rate of polymerization of lactide is proportional to the monomer and catalyst ('active centers') concentration. Consequently at very low catalyst levels the reaction rate will be very small, leading to low molecular weight polymer and a corresponding low percentage yield. At higher catalyst levels the reaction rate increases and high molecular weight and percentage yield are obtained. This corresponds to the ascending part of the curves in Figs 3 and 4. A further increase in catalyst concentration causes a too rapid reaction rate, resulting in a sudden molecular weight build up followed immediately after by a molecular weight decline indicating that depolymerization has taken place. Sn^{2+} is known to cause depolymerization as well as polymerization (Gilding and Reed, 1979).

Small amounts of an alcohol, such as lauryl alcohol, have been reported to act as accelerators for the reaction at the outset and as molecular weight controller, preventing depolymerization, in the later stages of the polymerization (Schmitt et al., 1969). However, the inclusion of lauryl alcohol in the polymerization mixture has recently been reported to have no evident effect (Rak et al., 1985). When lauryl alcohol was incorporated in our polymerization mixture (Table 3), increasing the co-catalyst level caused both a lowering of molecular weight and percentage yield.

The effect of polymerization time was studied at both 130°C and 190°C using optimum catalyst concentrations (Figs 5 and 6). The molecular weight continued to increase throughout the reaction (up to 4 h) indicating that the polymerization was not a chain reaction in the kinetic sense. This becomes more obvious when the inherent viscosity is plotted against percentage yield. The molecular weight continues to increase at conversions higher

TABLE 2

Effect of catalyst concentration on percentage yield of polymerization

	% Stannous octoate	90:10 [a]	70:30
130 °C (4 h)	0.02	21.0	66.6
	0.05	84.6	84.6
	0.1	94.5	97.6
	0.2	96.3	95.0
	0.5	86.1	88.2
190 °C (4 h)	0.005	8.0	32.0
	0.02	93.1	81.2
	0.03	98.0	92.4
	0.05	90.3	73.5
	0.1	84.0	70.0

[a] Lactide : glycolide initial w/w ratio.

TABLE 3

Effect of co-catalyst concentration on the molecular weight (iv) of the copolymer and on the percentage yield of the polymerization

% Lauryl alcohol (w/w)	iv (dl/g)	% Yield
0	0.663	98.3
0.01	0.612	91.4
0.05	0.462	88.3

Polymerization conditions: 0.03% stannous octoate, 4 h, 190°C, 90 : 10 initial lactide : glycolide ratio (w/w).

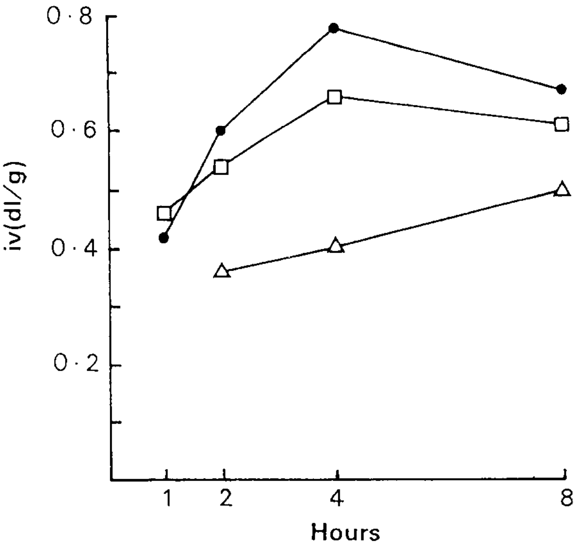


Fig. 5. Effect of reaction time on polymer molecular weight: (●) 0.1% catalyst, 130°C; (□) 0.03% catalyst, 190°C; (△) 0.03% catalyst, 130°C.

than 90%, regardless of the temperature of the reaction (Fig. 7).

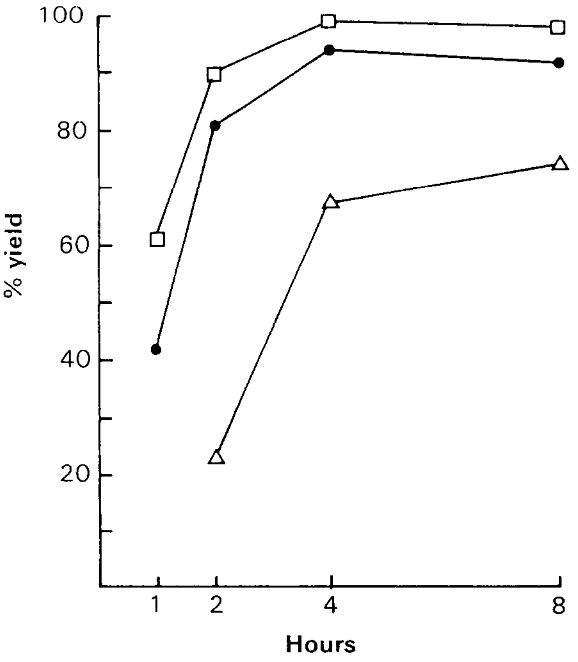


Fig. 6. Effect of reaction time on % yield of polymerization. Symbols as in Fig. 5.

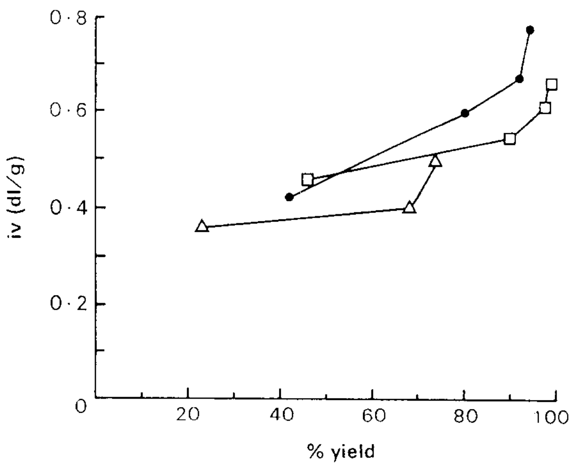


Fig. 7. Molecular weight of 90:10 (initial lactide:glycolide ratio w/w) copolymers vs % yield of the polymerization. Symbols as in Fig. 5.

At optimum catalyst levels the percentage yield remains essentially constant after 4 h reaction, but the molecular weight falls indicating depolymerization. When a lower than optimum level of catalyst is employed the molecular weight and percentage yield are still increasing after the 4 h period (Figs 5 and 6).

The time of polymerization may be expected to affect the composition of the resulting copolymer because glycolide, being more reactive, will be preferentially polymerized in the initial stages whilst lactide will be incorporated to an ever increasing extent as the glycolide is depleted. This will be important for medical use as the composition of the copolymer affects the rate of drug release through its effect on polymer hydrophilicity and degradation. The composition of copolymers produced from different reaction times is given in Table 4. The proportion of glycolide in the copolymer falls as the time of polymerization increases. However, the composition of the copolymers remains essentially constant at reaction times longer than 4 h. This result, considered with the lowering of the molecular weight after the 4 h reaction period, indicates that the optimum polymerization time is probably 4 h.

The difference in reactivity between the two monomers could have a significant effect on the microstructure of the copolymer. It is to be expected that copolymers containing 'blocks' of gly-

TABLE 4

Effect of polymerization time on the copolymer composition

Time (h)	% Glycolic acid units	
	0.03% Catalyst, 190 °C	0.03% Catalyst, 130°C
1	17.5	-
2	16.2	21.6
4	13.9	17.7
8	13.9	16.9

Starting composition: 90:10 w/w lactide:glycolide (12.1% in glycolide mol).

colide will be produced rather than copolymers of a random stucture. The microstructure of the copolymer can affect its solubility in organic solvents, its rate of hydration and its rate of degradation (Dunn et al., 1988).

In order to investigate the microstructure of the copolymers produced in this study the method proposed by Hutchinson (1982) was employed. In this method the ^{13}C-NMR spectrum of the copolymer is examined. In a homogeneous (random) copolymer the resonance of the glycolic acid unit carbonyl carbon should appear as two doublets as a consequence of the four different approximately equally probable molecular environments in which this carbon atom can exist, namely GGG, LGG, GGL, LGL, (G, glycolic acid unit; L, lactic acid unit). In heterogeneous copolymers the sequence LGL is unlikely to occur so that one of the doublets in the spectrum appears as a singlet. Hutchinson (1982) argued that this glycolic acid unit carbonyl carbonyl carbon signal appeared as two singlets in the spectrum of heterogeneous copolymers. The ^{13}C-NMR spectra of all samples examined, regardless of composition, temperature and time of polymerization were of the form shown in Fig. 8. Thus it appears that the copolymers produced in this study are block copolymers. This result also indicates that the transesterification reactions — which have been previously shown to occur during the polymerization of lactide (Chabot et al., 1983) — did not result in detectable redistribution of glycolide units in the polymer chains.

The morphology of the samples was examined by DSC. Because dl-lactide was used, all copolymers produced were amorphous, showing only glass transition temperature (T_g) (Fig. 9). Amorphous, polymers are preferable in drug delivery since they can form monophasic matrixes with homogeneous dispersion of the active ingredient. As was expected an increase in the molecular weight increased the T_g. An increase in

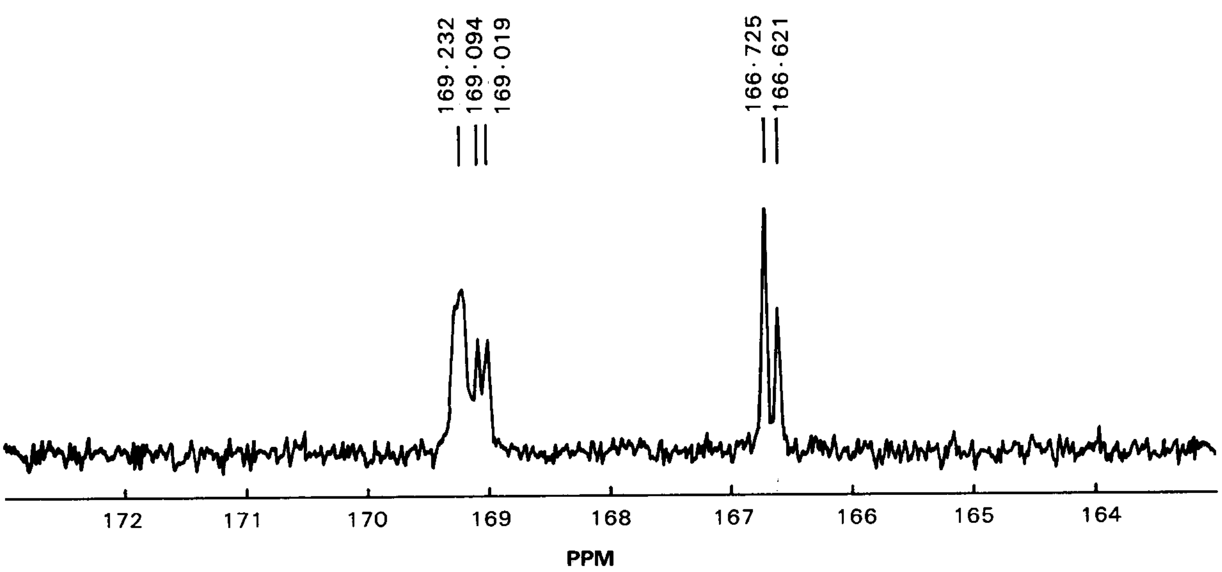


Fig. 8. ^{13}C-NMR spectrum of 70 : 30 (initial lactide : glycolide w/w ratio) copolymer in DMSO (resolution 1.017).

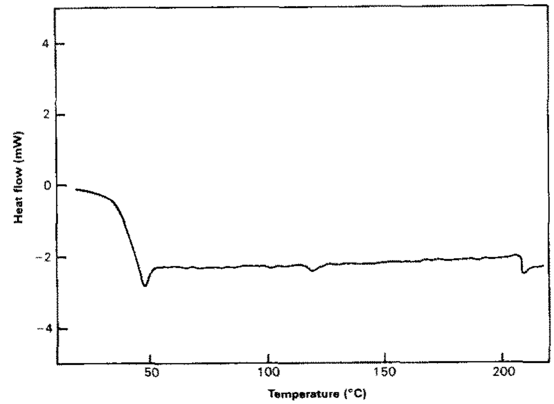


Fig. 9. DSC scan of 50:50 poly(lactide-co-glycolide) copolymer (iv = 0.5 dl/g).

the lactide content also caused an increase in the copolymer T_g (Table 5). This can be attributed to the increased difficulty of polymer molecule rotation caused by the increased number of methyl side groups.

It is important to note that glass transition temperatures as low as 37°C were observed with low molecular weight copolymers (Table 5). Moreover, Omelczuk et al. (1990) reported that low molecular weight poly(lactide) samples showed glass transition temperatures below 30°C. This implies that low molecular weight polymers could be above their T_g in the physiological environment and drug delivery systems made from such polymers would show significant differences in drug release rate from systems fabricated from high molecular weight polymers because free volume, permeability and chain mobility are higher above the T_g.

TABLE 5

Effect of molecular weight (iv) and composition of the copolymer on the glass transition temperature (°C) of the copolymer

Composition	iv (dl/g)				
	0.184	0.236	0.500	0.640	0.805
90:10 [a]	–	37	49	–	52
70:30	37	–	48	46	–
50:50	–	–	41	–	–

[a] Initial lactide: glycolide w/w ratio.

In conclusion it has been shown that the polymerization conditions affect the characteristics of the produced copolymer. It is possible that, by selecting the appropriate polymerization conditions, copolymers with properties suitable for the preparation of matrix tablets can be obtained.

References

Billmeyer, F.W., *Textbook of Polymer Science*, J Wiley, New York, 3rd Edn, 1984, p. 82.

Chabot, F., Vert, M., Chapelle, S. and Granger, P., Configurational structures of lactic acid stereocopolymers as determined by C−{H} n.m.r. *Polymer*, 24 (1983) 53–59.

Chujo, K., Kobayashi, H., Suzuki, J., Tokuhara, S. and Tanabe, M., Ring opening polymerization of glycolide. *Makromol. Chem.*, 100 (1967) 262–266.

Deasy, P.B., Finan, P.M. and Meegan, M.J., Preparation and characterization of lactic/glycolic acid polymers and copolymers. *J. Microencapsulation*, 6 (1989) 369–378.

Dittrich, W. and Schulz, R.C., Kinetic und Mechanisms der ringoffnenden Polymerization von l(−)-Lactid. *Ang. Makromol. Chem.*, 15 (1971) 109–126.

Dunn, R.L., English, J.P., Strobel, J.D., Cowsar, D.R. and Tice, T.R., Preparation and evaluation of lactide/glycolide copolymers for drug delivery. In Migliaresi, C., Nicolais, L., Giusti, P. and Chiellini, E. (Eds), *Polymers in Medicine III*, Elsevier, Amsterdam, 1988, pp. 149–160.

Frazza, E.J. and Schmitt, E.E., A new absorbable suture. *J. Biomed. Mater. Res.*, 1 (1971) 43–58.

Gilding, D.K. and Reed, A.M., Biodegradable polymers for use in surgery-polyglycolic/poly(lactic acid) homo- and copolymers: 1. *Polymer*, 20 (1979) 1459–1464.

Hutchinson, F.G., Continuous release pharmaceutical preparations. *Eur. Patent Appl.*, 82300416.3 (1982).

Kitchell, J.P. and Wise, D.L., Poly(lactic/glycolic) biodegradable drug-polymer matrix systems. *Methods Enzymol.*, 112 (1985) 436–448.

Lowe, C.E., Preparation of high molecular weight polyhydroxyacetic ester. *U.S. Patent*, 2668162 (1954).

Omelczuk, M.O., Chang, K.-T. and McGinity, J.W., Effect of thermal treatment on the physical-mechanical and dissolution properties of compacts containing biodegradable polymers. *9th Pharmaceutical Technology Conference*, Veldhoven, The Netherlands, 1990, Vol. 1, pp. 28–44.

Rak, J., Ford, J.L., Rostron, C. and Walters, V., The preparation and characterization of poly(d,l-lactic acid) for use as a biodegradable drug carrier. *Pharm. Acta Helv.*, 60 (1985) 162–169.

Schmitt, E.E., Epstein, M. and Polistina, R.A., Process for polymerizing a glycolide. *U.S. Patent*, 3422871 (1969).

Wise, D.L., Feldman, T.D., Sanderson, J.E. and Wentworth, R.L., Lactic/glycolic acid polymers. In Gregoriadis, G. (Ed.), *Drug Carriers in Biology and Medicine*, Academic Press, New York, 1979, pp. 237–270.