JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE 10 (1999) 29–33

Synthesis and properties of poly(lactic acid)

A. G. ANDREOPOULOS, E. HATZI, M. DOXASTAKIS
Department of Chemical Engineering, National Technical University of Athens, 9 Iroon Polytechniou Str., 157 80 Zografou, Greece

Poly(D,L lactic acid) was prepared by bulk polymerization of D,L lactide, both under atmospheric pressure and in vacuum. The obtained polymeric products were characterized in terms of molecular weight, M_w, melting point, calorimetric response and swelling behaviour. All products were amorphous. Their molecular weights were determined by viscosimetry and ranged from 2×10^3 to 9×10^4. Similarly, the melting points ranged from 90 to 210 °C. Swelling experiments, with specimens immersed in buffer solutions, showed that hydrolytic degradation started in a few days for the low M_w material, whereas for the higher molecular weight products it took much longer and probably followed a two-stage mechanism. This study suggests that the high molecular weight material could be an interesting carrier for the preparation of controlled release products, in cases where prolonged delivery is necessary.

1. Introduction

Degradable biomedical polymers are an interesting class of materials that can decompose to non-toxic products and find wide practical applications in medicine as implants or drug carriers. Typical examples are polymers deriving from polycondensation of lactic, glycolic and hydroxybutyric acid [1, 2]. More recently biodegradable pseudolatexes of poly(ε-caprolactone) were prepared and studied as potential aqueous coatings for sustained release [3].

Poly(lactic acid) is biocompatible and undergoes scission in the body, to monomeric units of lactic acid, which is a natural intermediate in carbohydrate metabolism. These characteristics make this polymer suitable for use in resorbable sutures, carriers for the controlled release of drugs, implants for orthopaedic surgery or blood vessels, which finally can be replaced by the body's tissues [4]. Mechanical properties that are directly affected by molecular weight of the polymer, are more or less critical depending on the application. More specifically, the preparation of slabs for use in controlled release does not require high strength and, therefore, low molecular weight material can be used. On the other hand, the construction of screws and plates for use as orthopaedic implants needs tough, high molecular weight material.

A great variety of polymeric systems have been studied as matrices for carrying and delivering drugs to a desired region of the body. Thus, for parenteral controlled release systems, biodegradable polymers have been shown to be advantageous compared with conventional polymers as they do not require surgical retrieval from the body after completion of the release. Poly(lactic acid) (PLA), with its crystalline L and amorphous D,L optical isomers, has been the subject of appreciable work. The use of these polymers for delivery of progesterone [5] and fertility control agents, preparations of vitamin D [6] or even for fluoride containing oral tablets [7] has also been reported. Regarding their degradation mechanism D,L PLA, together with other aliphatic polyesters have been tested *in vivo* and a non-enzymatic random hydrolytic chain scission established [8]. Similar results were obtained by *in vivo* and *in vitro* studies of the bioerosion of high molecular weight L PLA [9], which showed an increase in crystallinity upon degradation.

The zero-order release is a well desired fact and strongly dependent on the degradation pathway. PLA is reported to undergo both surface and bulk erosion, which probably disturbs an even rate of drug delivery [10]. Mixtures of high and low molecular weight polymer have been examined for their release properties and an acceleration in the rate was found from microspheres and films [11]. Studies on the effect of the molecular weight of D,L PLA on the release of theophylline showed that the rate decreases as molecular weight increases up to 138 000 [12].

The configuration of specific drug delivery systems has attracted the interest of many researchers. Thus, microspheres of L PLA [13, 14], D,L PLA [15] and poly(lactide-co-glycolide) [16] were prepared by various techniques, such as solvent evaporation and spray drying. Microspheres of biodegradable polymers containing the desired drug can be injected into the body with standard syringes. Other configurations including slabs [17], pellets [18], tablets [19], reservoir-type microcapsules [20] or coated films [21] have also been prepared.

Due to some weaknesses of the above systems, i.e. the need of surgical implantation for slabs and the poor retention in certain injection sites for microspheres, an *in situ* forming drug delivery system has

been proposed. It is essentially a solution of a biodegradable polyester or copolyester in *N*-methyl-2-pyrrolidone, containing the appropriate drug [22] and is suitable for intramuscular injection. Upon contact with body fluids this system can be solidified and serves as a drug delivery system. Furthermore, injectable systems based on low melting poly (D,L lactic acid) plasticized with propylene glycol have been proposed [23], as well as lactic acid oligomer microspheres containing anticancer agents for tumour targeting [24]. Low molecular weight polylactic acid microspheres have also been used as antibiotic carriers in the local treatment of osteomyelitis [25]. Local release has been clinically practised so far only with non-degradable carrier materials such as PMMA, which have the disadvantage of needing a second surgical procedure for their removal. Implants based on low molecular weight polylactic acid have the advantage of releasing the entire load of antibiotics during the degradation time [26].

The production of high strength PLA has also been described [27, 28]. L,L dilactide was used as a raw material with stannous 2-ethyl-hexanoate as the catalyst, and polymerization was carried out in vacuum (1.33×10^{-5} Pa) [29]. This method gave extremely high molecular weight (up to 1×10^6 determined by viscosimetry) PLA that was used for the preparation of implants. Those products were tested *in vivo* and showed to be suitable for application in maxillofacial surgery [30]. The use of PLA resorbable pins for fixation of fractures and osteotomies was also reported [31] whereas poly(glycolic acid) rods and pins gave successful results in the fixation of wrist fractures [32] and supracondylar fracture of the humerus [33]. Self-reinforced poly-L-lactide screws [34] and rods [35] have also been used in the fixation of cortical and cancellus bone osteotomies [36].

In this work an attempt was made to prepare high molecular weight poly(lactic acid) starting from the dilactide, because previous work showed that working with monomeric lactic acid cannot lead to those products [37–39]. As mentioned above, PLA with high molecular weight has improved mechanical properties and, therefore, it can be used as an implant in cases that require high strength and modulus. Futhermore, this type of polymer is expected to display an extended lifetime during its biodegradation, compared with that of the low molecular weight polymer. It should, therefore, be interesting to study the high molecular weight product for its potential use as a carrier for controlled release, capable of delivering a drug for a period of several months. As a matter of fact, previous investigations with the low molecular weight material showed that release lasts only a few weeks [40, 41] and consequently more stable polymers are necessary if we need prolonged delivery.

2. Experimental procedure

2.1. Materials

D,L-lactide (Boehringer) was used. Stannous-2-ethyl-hexanoate (Stannous octoate approximately 95%, Sigma) was used as a catalyst without further purification. The solvents used, i.e. toluene dichloroethane, methanol and ethyl acetate, were chemically pure (Merck).

2.2. Bulk polymerization under atmospheric pressure

Poly(D,L-lactide) was prepared by ring-opening bulk polymerization of D,L-lactide that was previously recrystallized from ethyl acetate and dried at 50 °C for approximately 20 h. The monomer was placed in a 100 ml Erlenmeyer flask and the initiator (0.01–0.12 wt %) was added as a 0.5% w/v solution in toluene. The reaction vessel was sealed with a glass stopper and immersed into a thermostatically controlled oil bath at 140 °C for 20 h. The polymerization product was then dissolved in dichloromethane and precipitated with methanol.

2.3. Bulk polymerization under vacuum

The ring-opening polymerization of D,L-lactide was performed after purification of the monomer by recrystallization from ethyl acetate. Some 0–150 p.p.m. of stannous octoate were added in the mixture, as above, in order to catalyse the polymerization reaction. The reaction vessels were sealed under vacuum (1.33×10^{-4} Pa) and placed in an oil bath at 140 and 130 °C for 20 h. The product was again dissolved in dichloromethane and precipitated in methanol.

2.4. Physicochemical characterization

The molecular weight of the polymerized materials was determined by viscosimetry using ubbelhode viscometers placed in a waterbath thermostatically controlled at 25 °C. The polymerization products were dissolved in chloroform at concentrations ranging from 0.2 to 2 g dl^{-1}. Calculations were made using the Mark–Houwink equation

$$[n] = KM_w^a$$

where $[n]$ is the limiting viscosity number, M_w the viscosity average molecular weight, and the constants $K = 2.21 \times 10^{-4}$ and $a = 0.77$.

The melting temperatures of the polymers prepared were determined by visual control of a capillary glass tube filled with powder of the polymer and placed in the appropriate apparatus capable of raising the temperature at a slow rate. Because poly(D,L-lactic acid) is amorphous its melting temperature cannot be defined as a sharp point, but rather it is a region. Therefore, the recorded melting points correspond to the temperature where the polymer particles change their shape to drops and turn to a liquid.

Additional information about the transitions of the polymers produced upon heating can be obtained by differential scanning calorimetry (DSC) tests. DSC was performed using a Perkin–Elmer DSC-4/TADS calorimeter, at a heating rate of 10 °C min^{-1}. Scans were run in the range 50–300 °C.

Finally, the swelling behaviour of specimens in a buffer solution (pH 7.2) was studied, as it is a critical

parameter that describes their performance in delivering drugs. Specimens were compression moulded in a hydraulic press, into discs 10 mm in diameter and 2.8 mm thick. Swelling was recorded with time, as the percentage of weight gain of the specimens immersed in the buffer solution.

3. Results and discussion

The effect of the catalyst concentration on molecular weight of the polymer are given in Table I. The results suggest that molecular weight is strongly dependent on the amount of catalyst present in the reaction mixture. When small concentrations of stannous octoate (0.01–0.03%) are used, the degree of polymerization is low. As the catalyst concentration increases up to 0.12%, the molecular weight shows a significant increase and exceeds 90 000. It is worth mentioning that D,L-lactide polymerization is extremely sensitive to the presence of hydroxyl groups that act as chain transfer agents. The most likely sources of hydroxyl groups are impurities in D,L-lactide, such as lactoyl lactic acid, lactic acid and absorbed moisture, because lactide and stannous octoate are hygroscopic substances. For this reason, in order to obtain reproducible results, many parameters have to be under tight control, such as purification of D,L-lactide, pretreatment of the reaction vessels, reaction conditions (time, temperature, pressure).

When vacuum was applied, smaller amounts of stannous octoate gave much higher molecular weight, as can be seen in Fig. 1. It is clear that molecular weight increases linearly with catalyst concentration and shows a limiting effect after 150 p.p.m. of stannous octoate.

TABLE I The molecular weight of PLA obtained at various concentrations of catalyst

$Sn(Oct)_2$ (wt %)	Molecular weight (M_w)
0.03	4500
0.05–0.06	10 000–11 500
0.07–0.08	17 000–32 000
0.09–0.12	80 000–90 000

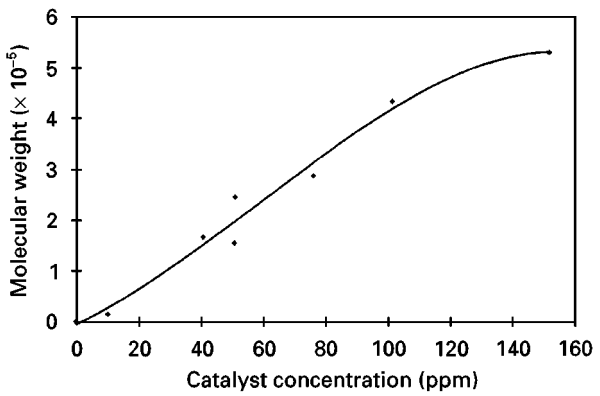

Figure 1 The relationship between the viscosity–average molecular weight of PLA and the catalyst concentration.

The effect of molecular weight on the melting temperatures of various samples is shown in Fig. 2. It is evident again that increased molecular weight corresponds to more heat stable products and this relationship tends to be linear within the range of the molecular weight obtained. The melting behaviour of the polymers prepared is a very important factor for their potential use as carriers for the controlled release of drugs. In fact, drugs incorporated into the poly(lactic acid) by a melting process must be stable enough to withstand temperatures up to 100 °C. This limit corresponds to polymers with relatively low molecular weight (2×10^3–3×10^3). In cases where we need a carrier with higher molecular weight, for reasons of mechanical strength or slower biodegradation, it is more safe to incorporate the drug by another technique, e.g. dissolution, which ensures minimal exposure to high temperature.

Related to the above are the data obtained from the DSC thermograms, which clearly show the amorphous characters of the polymers obtained. Therefore, in Fig. 3 no endotherms can be observed suggesting transitions or melting. At high temperature, the degradation of the polymer is likely to produce deviations from the base line.

The swelling capacity of products prepared in this work with varying molecular weight, is presented in Figs 4–8. Fig. 4 shows the swelling behaviour of specimens with the lowest molecular weight. It is evident

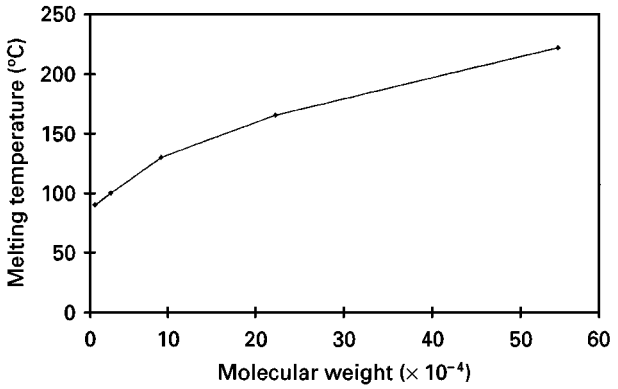

Figure 2 Melting temperature as a function of molecular weight, M_w, of various PLA samples.

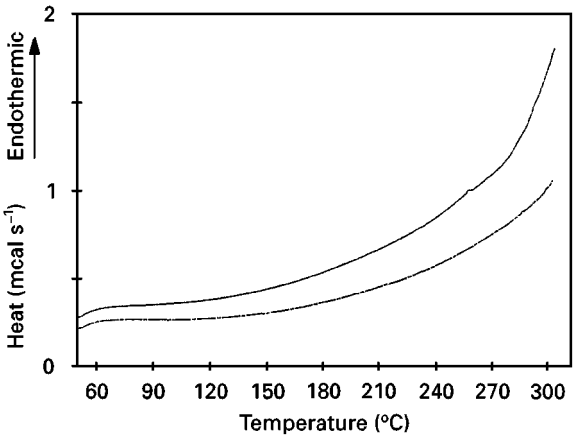

Figure 3 DSC patterns for PLA samples.

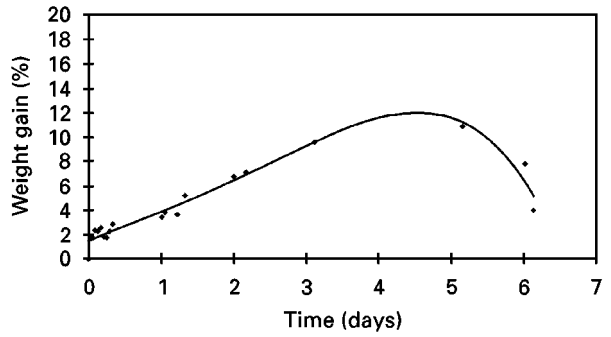

Figure 4 Swelling of PLA sample ($M_w = 2000$) in buffer (pH 7.2).

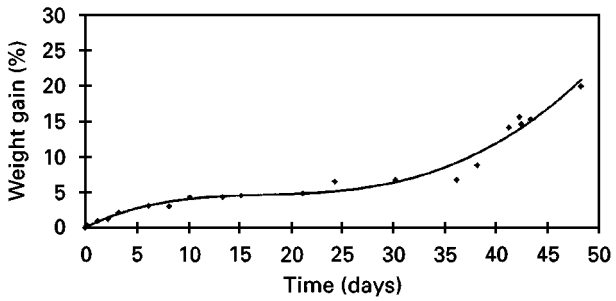

Figure 5 Swelling of PLA sample ($M_w = 12\,700$) in buffer (pH 7.2).

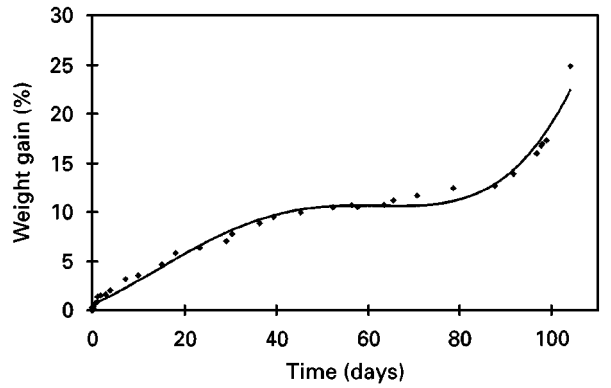

Figure 6 Swelling of PLA sample ($M_w = 32\,700$) in buffer (pH 7.2).

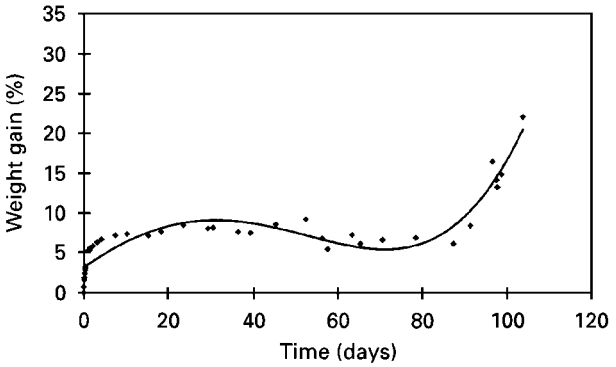

Figure 7 Swelling of PLA sample ($M_w = 58\,000$) in buffer (pH 7.2).

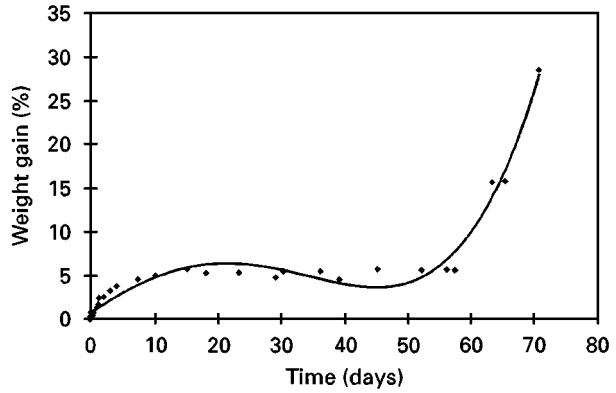

Figure 8 Swelling of PLA sample ($M_w = 90\,800$) in buffer (pH 7.2).

that water uptake proceeds linearly during the first four–five days. Then, significant weight loss is observed, obviously due to the fact that the rate of hydrolytic degradation becomes high enough beyond this time.

As the molecular weight increases to $M_w = 12\,700$, a different type of swelling curve is produced (Fig. 5). In that case, water sorption proceeds for the first 15 days at a rate much lower than that of the specimen with $M_w = 2000$. Then equilibrium is achieved for the next 15 days. This reflects that the rates of swelling and degradation became equal during this period, so that no changes in weight are observed. Very interestingly, a second swelling stage emerges after this point, where an increased rate of water uptake is recorded. This probably suggests that degradation of the higher molecular weight polymer leads to a modified product that is more susceptible to swelling even compared with the polymer of lowest molecular weight, $M_w = 2000$. It should be taken into consideration that a random depolymerization reaction that takes place with condensation of the polymer, such as polylactide, usually produces chain fragments with varying lengths. Therefore, the polydispersity of the swollen sample is likely to be very different than that of the starting material because its molecular weight distribution is drastically changed. As a result, there is a change in the swelling behaviour.

The same pattern can be observed in Figs 6, 7 and 8, where the swelling behaviour of specimens with molecular weights of 32 700, 58 000 and 90 800, respectively, is presented. The above–mentioned mechanism of hydrolytic depolymerization of polylactide, is probably responsible for the different swelling rate of the polymers with higher molecular weight. These variations must be taken into account when those polymers are evaluated as potential drug carriers. In fact, swelling and degradation are both important processes for controlling the release rate of drugs. It is obvious that the high molecular poly(lactic acid) prepared in this work would be suitable for prolonged drug delivery. However, the rate of release in such systems needs to be studied in detail before adopting a certain product for this application because particular release characteristics are usually necessary, e.g. zero-order release.

4. Conclusions

D,L lactide is a suitable starting material for the preparation of high molecular weight poly(lactic acid), provided that care is taken for its purification. Polymerization in vacuum gives better results in terms of reproducibility and molecular weight. Amorphous products are obtained with melting temperatures up to 210 °C. The swelling behaviour of products with high molecular weight is significantly different than that of poly(lactic acid) with $M_w = 2000$ and therefore, the use of the former product in controlled release could ensure prolonged drug delivery. For this application, further study is necessary in order to define the kinetics of release.

Acknowledgements

The authors wish to thank Drs G. Entenmann and H. Liedtke from Boehringer Ingelheim KG, who kindly supplied us with raw materials for our work.

References

1. R. J. M. ZWIERS, S. GOGOLEWSKI and A. J. PENNINGS, *Polymer* **24** (1983) 167.
2. P. GRECO and E. MARTUSCELLI, *ibid.* **30** (1989) 1475.
3. M. D. COFFIN and J. W. McGINITY, *Pharm. Res.* **9** (1992) 200.
4. B. ELING, S. GOGOLEWSKI and A. J. PENNINGS, *Polymer* **2** (1982) 1587.
5. L. R. BECK, D. R. COWSAR, D. H. LEWIS, R. J. COSGRAVE, C. T. RIDDLE, S. L. LOWRY and T. E. EPPERLY, *Fertility Sterility* **5** (1979) 545.
6. I. GENTA, I. F. PAVANETTO, B. CONTI and P. GIUNCHEDI, *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.* **18** (1991) 676, edited by Controlled Release Society, Inc., Deerfield Illinois, USA, pp. 905, Amsterdam, Netherlands, July 8–11, 1991.
7. P. BOTTENBERG, C. DE MUYNCK, S. BOUCKAERT, D. COOMANS, D. SLOP and J. P. REMON, *ibid.* **18** (1991) 631.
8. C. G. PITT, M. M. GRATZL, G. M. KIMMER, J. SURLES and A. SCHINDLER, *Biomaterials* **2** (1981) 215.
9. J. W. LEENSLAG, A. J. PENNINGS, R. R. M. BOS, F. R. ROZEMA and G. BOERING, *ibid.* **8** (1987) 311.
10. C. SHIH, T. HIGUCHI and K. J. HIMMELSTEIN, *ibid.* **5** (1984) 237.
11. R. BODMEIER, K. H. OH and H. CHEN, *Int. J. Pharm.* **51** (1989) 1.
12. M. O. OMELCZUK, and J. W. McGINITY, *J. Pharm. Res.* **9** (1992) 26.
13. R. WADA, S. H. HYON and Y. J. IKADA, *Pharm. Sci.* **79** (1990) 919.
14. A. KISHIDA, J. B. DRESSMAN, S. YOSHIOKA, Y. ASO and Y. TAKEDA, *J. Control. Rel.* **13** (1990) 83.
15. B. W. BRUHN and B. W. MILLER, *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.* **18** (1991) 668, edited by Controlled Release Society, Inc., Deerfield Illinois, USA, pp. 905, Amsterdam, Netherlands, July 8–11, 1991.
16. T. R. TICE, R. M. GILLEY, D. F. LOVE, F. LABRIE and D. W. MASON, *ibid.* **18** (1991) 467.
17. G. WEI, Y. KOTOURA, M. OKA, T. YAMAMURO, R. WADA, S. H. HYON and Y. IKADA, *J. Bone Joint Surg. Br.* **73-B** (1991) 246.
18. R. BODMEIER and H. CHEN, *J. Pharm. Sci.* **78** (1989) 819.
19. K. AVGOUSTAKIS and J. R. NIXON, *Int. J. Pharm.* **70** (1991) 77.
20. A. DEMIRDERE, T. KISSEL, U. SIEMANN and H. SUCKER, *Eur. J. Pharm. Biopharm.* **37** (1991) 42.
21. T. G. PARK, S. COHEN and R. LANGERR, *Pharm. Res.* **9** (1992) 37.
22. R. L. DUNN, J. M. A. TIPTON and E. M. MENARDI, *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.* **18** (1991) 465, edited by Controlled Release Society, Inc., Deerfield Illinois, USA, pp. 905, Amsterdam, Netherlands, July 8–11, 1991.
23. A. G. ANDREOPOULOS, *Clin. Mater.* **15** (1993) 89.
24. C. SAKAKURA, T. TAKAHASHI, A. HAGIWARA, M. ITOH, T. SASABE, M. LEE and S. SHOBAYASHI, *J. Control. Rel.* **22** (1992) 69.
25. X. ZHANG, U. P. WYSS, D. PICHORA and M. F. A. GOOSEN, *J. Pharm. Pharmacol.* **46** (1994) 718.
26. C. SCHMIDT, R. WENZ, B. NIES and F. MOLL, *J. Control. Rel.* **37** (1995) 83.
27. J. W. LEENSLAG and A. J. PENNINGS, *Polym. Comm.* **28** (1987) 92.
28. H. R. KRICHELDORF, I. KREISER-SAUNDERS and C. BOETTCHER, *Polymer* **36** (1995) 1253.
29. J. W. LEENSLAG and A. J. PENNINGS, *J. Makromol. Chem.* **188** (1987) 1809.
30. J. W. LEENSLAG, A. J. PENNINGS, R. R. M. BOS, F. R. ROZEMA and G. BOERING, *Biomaterials* **8** (1987) 70.
31. O. PHILAJAMAKI, O. BOSTAMAN, E. HIRVENSALO, P. TORMALA and P. ROKKANEN, *J. Bone Joint Surg. Br.*, **74-B** (1992) 853.
32. P. P. CASTELEYN, F. HANDELBERG and P. HAENTJENS, *ibid.* **74-B** (1992) 858.
33. R. K. FRASER and W. G. COLE, *ibid.* **74-B** (1992) 929.
34. M. J. MANNINEN, *J. Mater. Sci. Mater. Med.* **4** (1993) 179.
35. M. J. MANNINEN and T. POHJONEN, *Biomaterials* **14** (1993) 305.
36. M. J. MANNINEN, U. PAIVARINTA, H. PATIALA, P. ROKKANEN, R. TAURIO, M. TAMMINMAKI and P. TORMALA, *J. Mater. Sci. Mater. Med.* **3** (1992) 245.
37. E. C. HATZI, PhD thesis, National Technical University of Athens, Athens (1997).
38. J. MAUDUIT, N. BUKH and M. VERT, *J. Control. Rel.* **23** (1993) 209.
39. M. VERT, G. SCHWARCH and J. COUDANE, *J. Mater. Sci. Pure Appl. Chem.* **A32** (1995) 787.
40. A. G. ANDREOPOULOS, *J. Biomed. Appl.* **10** (1995) 163.
41. A. G. ANDREOPOULOS, T. KORAKIS, E. DOUNIS, K. KANELLAKOPOULOU, A. ANASTASIADIS and P. TZIVELEKIS, *ibid.* **10** (1996) 338.

Received 9 October 1997
and accepted 26 January 1998