Controlled release of salicylic acid from poly(D,L-Lactide)

A.G. ANDREOPOULOS, E. HATZI, M. DOXASTAKIS
Department of Chemical Engineering, National Technical University of Athens, 9 Iroon Polytechniou Str., 15780 Zografos, Greece
E-mail: andreo@chemeng.ntua.gr

Poly(D,L-Lactide) of high molecular weight (M_v) was prepared by ring-opening bulk polymerization of D,L-Lactide and characterized in terms of M_v, melting point and swelling behavior in buffer solution. Samples of the polymers with low and high M_v (2000 and 22 000 respectively) loaded with various amounts of salicylic acid (SA) were immersed in a buffer solution and the release of SA was recorded. The results obtained showed that swelling of the poly(D,L-Lactide) samples obeyed Fick's law, especially for those with high molecular weight, where biodegradation proceeds slowly. The release of SA seemed to follow a simplified relationship which is linear with time, at least for the early stages of delivery. The extent of linearity is dependent on the content of the acidic SA, which probably accelerates decomposition of the high molecular weight products.

1. Introduction

Recent developments in the field of sustained release of drugs have shown the great importance of biodegradable plastics as materials for carrying and delivering drugs to a certain region of the body. In fact, many biodegradables can decompose to non-toxic, readily bioresorbable products and therefore they are tolerated by the human organism. In addition, biodegradation gives them an advantage over conventional non-degradable biomaterials because, once implanted, they do not require surgical retrieval from the body after completion of the release.

Some representatives of this class of biomaterials are polymers deriving from polycondensation of lactic, glycolic and hydroxybutyric acid [1, 2]. Also, pseudolatexes of poly/ε-caprolactone) were prepared and studied as potential aqueous coatings for sustained release [3].

Poly(lactic acid) (PLA) is perhaps the most studied material for this application 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 further uses such as resorbable sutures, implants for orthopedic surgery or blood vessels, which finally can be replaced by the body's tissues [4]. As to the sustained release, PLA has been used for delivery of antimycobacterial drugs [5], quinolones [6], antimalarial [7] and anti-inflammatory drugs [8], antitumor agents [9], hormones [10] and fluoride containing tablets for oral use [11].

The mechanical properties of PLA, which are directly affected by the molecular weight of the polymer, are more or less critical depending on the application. In fact, 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 orthopedic implants needs tough, high molecular weight material.

Many works dealt with the preparation of high strength PLA starting form the di-lactide with stannous 2-ethyl-hexanoate as catalyst and running the polymerization in vacuum (10^{-7} torr) [12–14]. This method gave products with molecular weights of up to 1×10^6 which can be used for the preparation of implants. Those products were tested *in vivo* and showed to be suitable for application in maxillofacial surgery [15]. The use of PLA resorbable pins for fixation of fractures and osteotomies was also reported [16] whereas poly(glycolic acid) rods and pins gave successful results in the fixation of wrist fractures [17] supracondylar fracture of the humerus [18]. Self-reinforced poly-L-Lactide screws [19] and rods [20] have also been used in the fixation of cortical and cancellus bone osteotomies [21].

In a previous work [22], an attempt was made to prepare high molecular weight poly (D,L-Lactide) starting from the D,L-dilactide, since it has been reported that working with monomeric lactic acid cannot lead to those products [23–25]. The polymeric products obtained were characterized in terms of molecular weight (M_v), melting point, calorimetric response and swelling behavior. Their viscosity average molecular weights ranged from 2×10^3 to 9×10^4 and the melting points from 90 to 210 °C. Swelling experiments, with specimens immersed in buffer solutions, showed that hydrolytic degradation starts in a few days for the low M_v material, whereas for the higher molecular weight products it takes much longer and probably follows a two-stage mechanism. The above study suggested that high molecular weight materials could be interesting carriers for the preparation of controlled release systems, where prolonged delivery is necessary. It seemed

therefore worth exploring the capabilities of the high molecular weight materials for drug delivery taking into account that the slow biodegradation rate leads to an increased role of the drug diffusion within the polymer matrix during the release procedure.

2. Theoretical background

Biodegradation is reported to cause polylactide surface and bulk erosion, which probably disturbs an even rate of release and more specifically, the well-desired behavior of the zero-order release [26]. Furthermore, the drug diffusion through the polymeric matrix is an additional mechanism contributing to the complexity of the phenomenon. However, some simplified models considering the matrix degradation as the only parameter which controls the release rate have been proposed, leading to simple relationships which describe the drug delivery, such as [27]:

$$dM_t/dt = K_o \times \text{surface area} \quad (1)$$

where M_t is the drug released at time t, and K_o is the heterogeneous degradation constant of the matrix.

With the assumption that the edge effects are neglected, the change in surface area as a function of time depends on the specimen geometry and is constant for a slab or disk, whereas for cylinders and spheres is: $2\pi L(\alpha - K_o t/C_o)$ and $4\pi(\alpha - K_o t/C_o)^2$ respectively, where C_o is the uniform initial drug concentration in the matrix and α the radius of cylinder or sphere. Thus, a single expression can be used to describe the release profile:

$$M_t/M_\infty = 1 - [1 - K_o t/C_o \alpha]^n \quad (2)$$

where M_∞ is the total amount of drug in the device, α the radius of cylinder or sphere or the half thickness of slab, where $n = 1$ for slab, 2 for a cylinder and 3 for a sphere, which gives a linear relationship versus time in the case of slab:

$$M_t/M_\infty = K_o t/C_o \alpha \quad (3)$$

3. Experimental procedure

3.1. Materials

D,L-Lactide was donated by Boehringer Ingelheim AG (Germany). Stannous-2-ethyl-hexanoate (Stannous octoate, approximately 95%, Sigma, Germany) was used as a catalyst without further purification. The solvents used, i.e. toluene dichloroethane, methanol and ethyl acetate were chemically pure and were purchased from Merck (Switzerland).

3.2. Bulk polymerization under atmospheric pressure

Poly(D,L-Lactide) was prepared by ring-opening bulk polymerization of D,L-Lactide which was previously recrystallized from ethyl acetate and dried at 50 °C for 20 h approximately. 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.

3.3. Bulk polymerization under vacuum

The ring-opening polymerization of D,L-Lactide was performed after purification of the monomer by recrystallization from ethyl acetate. 0–150 ppm of stannous octoate were added in the mixture, as above, in order to catalyze polymerization reaction. The reaction vessels were sealed under vacuum (10^{-6} mm Hg) and placed in an oil bath at 140 °C and at 130 °C for 20 h. The product was again dissolved in dichloromethane and precipitated in methanol.

3.4. 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. Calculations were made using the Mark-Houwink equation. $[n] = kM^a$, which determines the viscosity average molecular weight (M_v) via the limiting viscosity number [n], with the following 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. Since poly(D,L-Lactic acid) is amorphous, it can be better characterized by its glass transition temperature (T_g). However, the determination of melting temperature, which in fact cannot be defined as a sharp point but rather is a region, would be of importance for the further processing of the polymer obtained (e.g. blending with drugs etc). The recorded melting points correspond to the temperature where the polymer particles change their shape to drops and turn to a liquid.

Finally, the swelling behavior of specimens in a buffer solution (pH 7.2) was studied as it is a critical parameter for their performance in delivering drugs. Specimens were compression molded in a hydraulic press, into slabs of 10 mm diameter and 2.8 mm thick. Swelling was as the percentage of weight gain of the specimens immersed in the buffer solution.

3.5. Release of salicylic acid

Products with low and high average molecular weight (2000 and 22 000 respectively) were loaded with various amounts of SA and its delivery was recorded. SA is a convenient model compound with low water solubility and can be easily identified by its absorption peak in the uv spectrum at 298 nm [28]. SA was added and mixed to the melt of poly(D,L-Lactide) at concentrations varying from 1% to 10%. It should be noted that the melting points of the two types of polymers are 90 °C and 115 °C, for the low and high (M_v) respectively. Melting

temperature is a critical parameter when the incorporation of the drug is carried out by melt mixing, because heat unstable drugs can decompose when incorporated to high melting polymeric matrices.

After mixing, the melt was molded into slabs (10 mm diameter, 3 mm height), which were immersed in 100 ml of buffer solution with pH = 7.2, and kept at 37 °C. The release was followed by ultra-violet spectroscopy. Samples of 0.5–1 ml were taken at various time intervals and after dilution to 50 ml with distilled water, their absorption intensity was measured in a Hitachi U-1100 (Japan) uv-vis spectrophotomer, at 298 nm.

4. Results and discussion

The sorption curves for the two types of samples are shown in Figs 1 and 2, in terms of M_t/M_∞ versus the square root of time. These expressions were selected in order to examine the applicability of the Fick's law [24], i.e.

$$M_t/M_\infty = 4/\pi[Dt/l^2]^{1/2} \quad (4)$$

where M_t and M_∞ are the amount of water sorbed at time t and equilibrium respectively; D the diffusion coefficient; and l the specimen thickness. From the curve of Fig. 1 it is clear that a linear $(R = 0,9815)$ dependence describes the sorption process of the high molecular weight samples, which suggests that water transport is controlled by diffusion. However, in Fig. 2 linearity cannot be observed even at the first stages of sorption $(R = 0,9296)$. This behavior can be attributed to some degradation of the low molecular weight material, which is reasonable to greatly influence the water transport procedure. Moreover, some changes in average molecular weight and the molecular weight distribution which were recorded upon biodegradation and are likely to strongly affect the value of the diffusion coefficient, D [22]. Due to the above reasons, in the case of low M_v PLA the measured weight is the result of an increase due to water sorption and a decrease due to degradation. Also, the ultimate amount of water sorbed cannot by expressed by M_∞, since equilibrium is not reached with this material. The stability of weight found after a few days, could simply suggest that the rate of sorption and degradation become equal at that time.

The release from the sample with $M_v = 2000$, loaded with 1% and 5% SA, can be seen in Figs 3 and 4 respectively. The delivery of SA is plotted in terms M_t/M_∞ versus time, where: M_t is the SA released at time t, and M_∞ the total amount of SA in the slab. In addition, the total amount of SA released at time t from these samples (initially containing 3 mg and 15 mg of SA respectively) is presented in Table I.

The expression M_t/M_∞ was used in order to determine whether linearity is established, which would suggest the applicability of Equation 3. That simplified version of a relationship describing the release of SA seemed reasonable to be expected since the specimens studied had the form of slabs.

As a matter of fact, a linear dependence can be observed for the early stages of release and continues up to 70–80% of the whole procedure for both samples. As expected, the sample containing 5% SA displays prolonged delivery compared with that loaded with 1% SA.

Similarly, delivery from samples with $M_v = 22\,000$, loaded with 1%, 5% and 10% SA, is shown in Figs 5–7, respectively. In this case again, the total amount of SA released at time from the above samples (initially

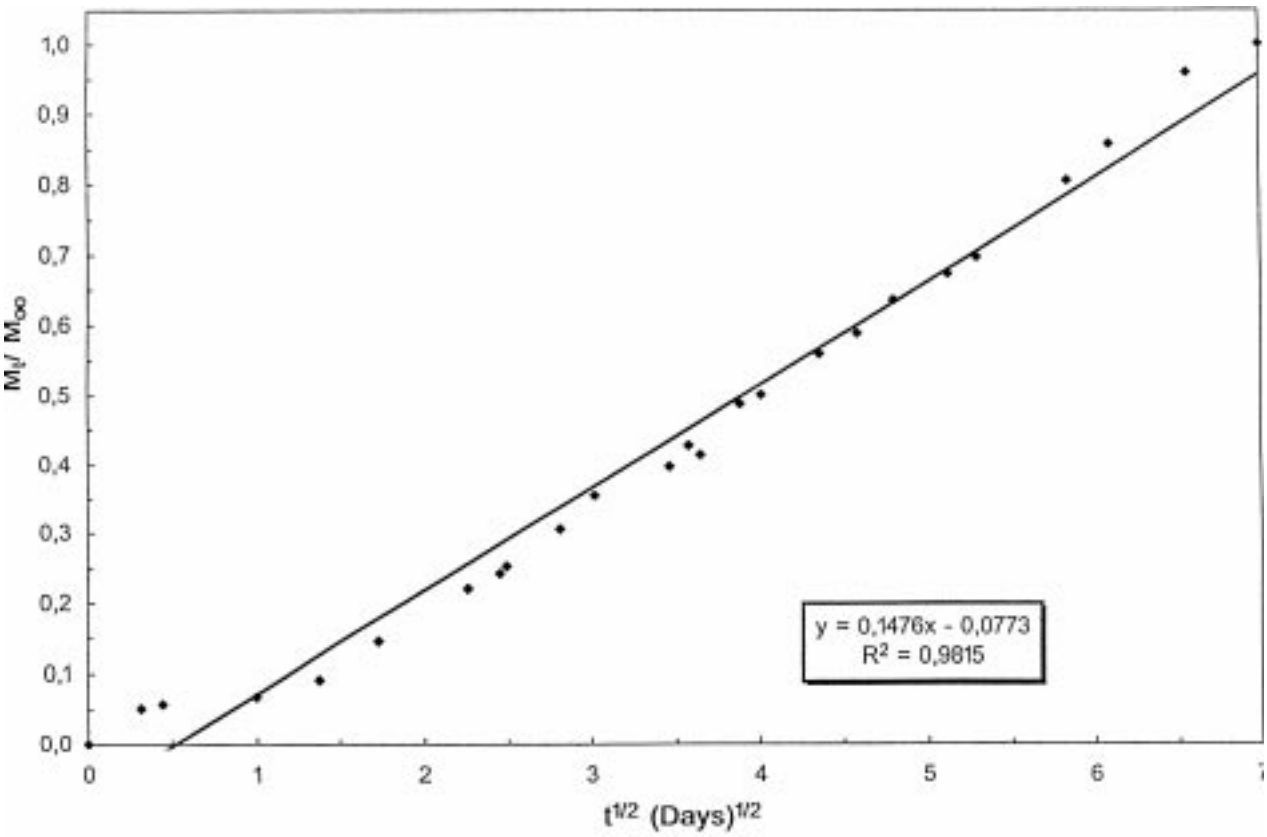

Figure 1 Swelling of poly(D,L-Lactide) $M_v = 22\,000$ in buffer solution, pH = 7.2.

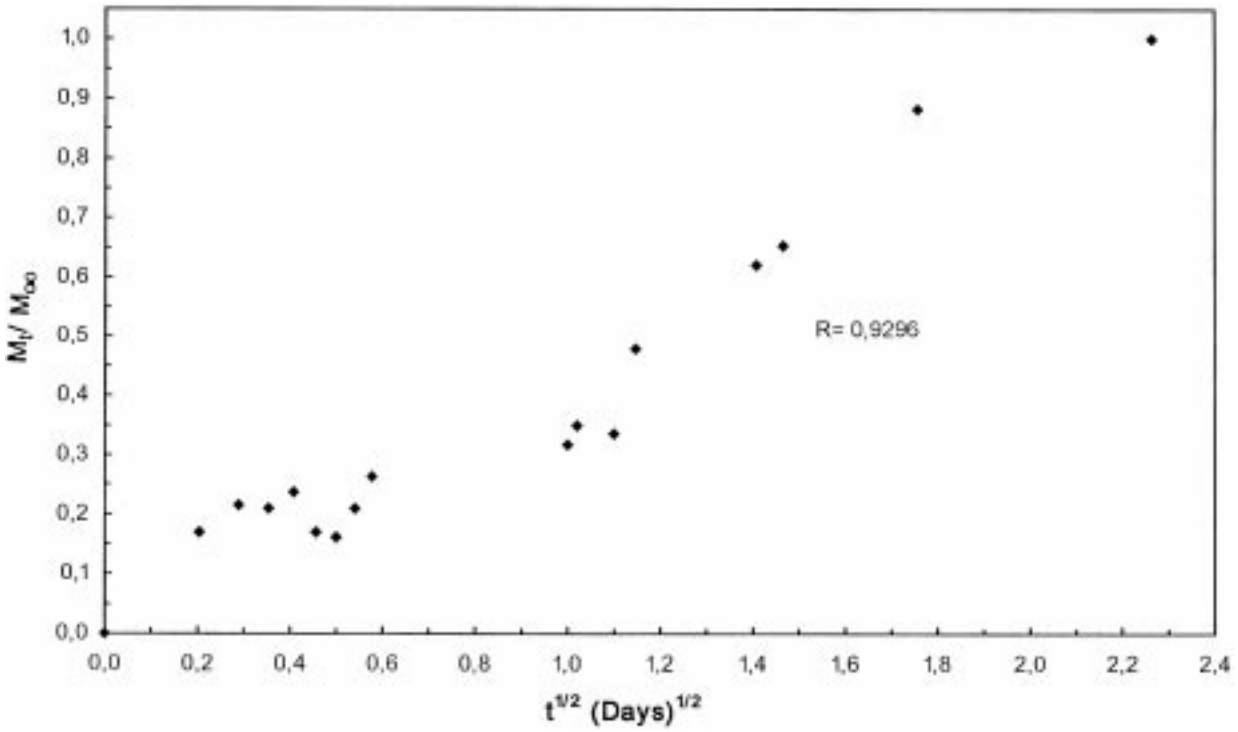

Figure 2 Swelling of poly(D,L-Lactide) $M_v = 2000$ in buffer solution, pH = 7.2.

containing 3 mg, 15 mg and 30 mg of SA respectively) is presented in Table II.

From the curves of Figs 5–7 it is clear again that linear relationship is established in the early stages of release. However, in this case, an evident influence of the concentration of SA on the extent of linearity can be observed. More specifically, for samples loaded with 1% SA the linear dependence applies to 35% of the release procedure, whereas for 5% SA it exceeds 50% and for 10% reaches 75%. Also, the release rate increases with increasing SA content. On the other hand, the total delivery time is the same for all three types of the samples studied. This behavior of the samples with $M_v = 22\,000$ could be explained taking into consideration some interactions of SA with the polymeric matrix of the biodegradable poly(D,L-Lactide). As a matter of fact, the hydrolysis is likely to be promoted by the presence of SA, i.e. an acidic substance with some solubility in water.

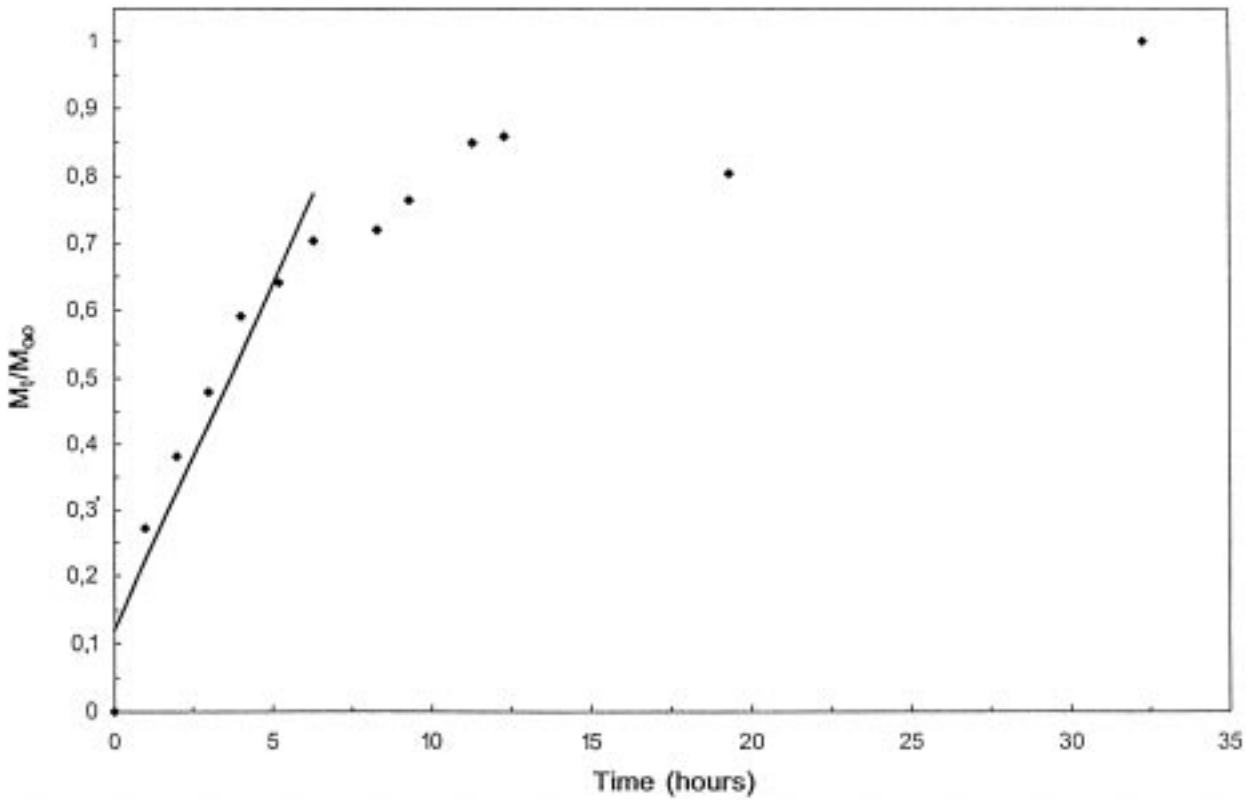

Figure 3 Release from poly(D,L-Lactide) $M_v = 2000$, loaded with 1% salicylic acid, in buffer solution.

TABLE I The weight of salicylic acid released at time t, from low M_v samples

Time (h)	Weight released (mg)	
	PLA-1% SA	PLA-5% SA
1	0,816	4,53
2	1,14	7,44
3	1,44	9,12
4	1,77	9,83
5	1,90	10,78
6	2,11	13,35
7	—	15
8	2,16	—
9	2,29	—
11	2,54	—
32	3	—

— : Not measured.

TABLE II The weight of salicylic acid released at time t, from samples with $M_v = 22\,000$

Time (h)	Weight released (mg)		
	PLA-SA 1%	PLA-SA 5%	PLA-SA 10%
1	0,057	—	1,02
2	0,315	2,1	4,44
2,9	0,366	—	4,59
4	0,51	—	5,28
6	0,573	—	9,33
9	—	5,8	
13	0,972	6,69	21,43
20	0,942	7,71	17,19
22	1,17	6,16	—
42	1,55	11,7	21,21
52	1,84	15	29,13
54	2,92	—	30
56	3	—	—

— : Not measured.

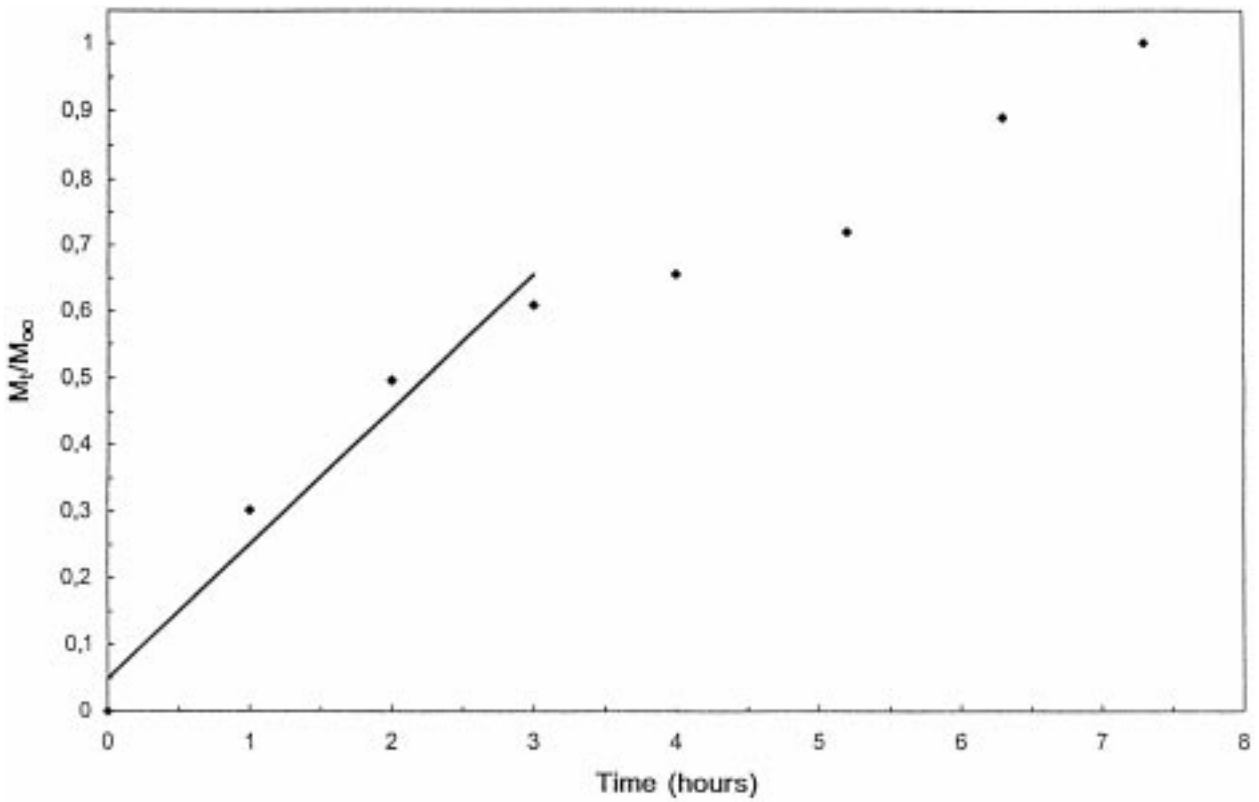

Figure 4 Release from poly(D,L-Lactide) $M_v = 2000$, loaded with 5% salicylic acid, in buffer solution.

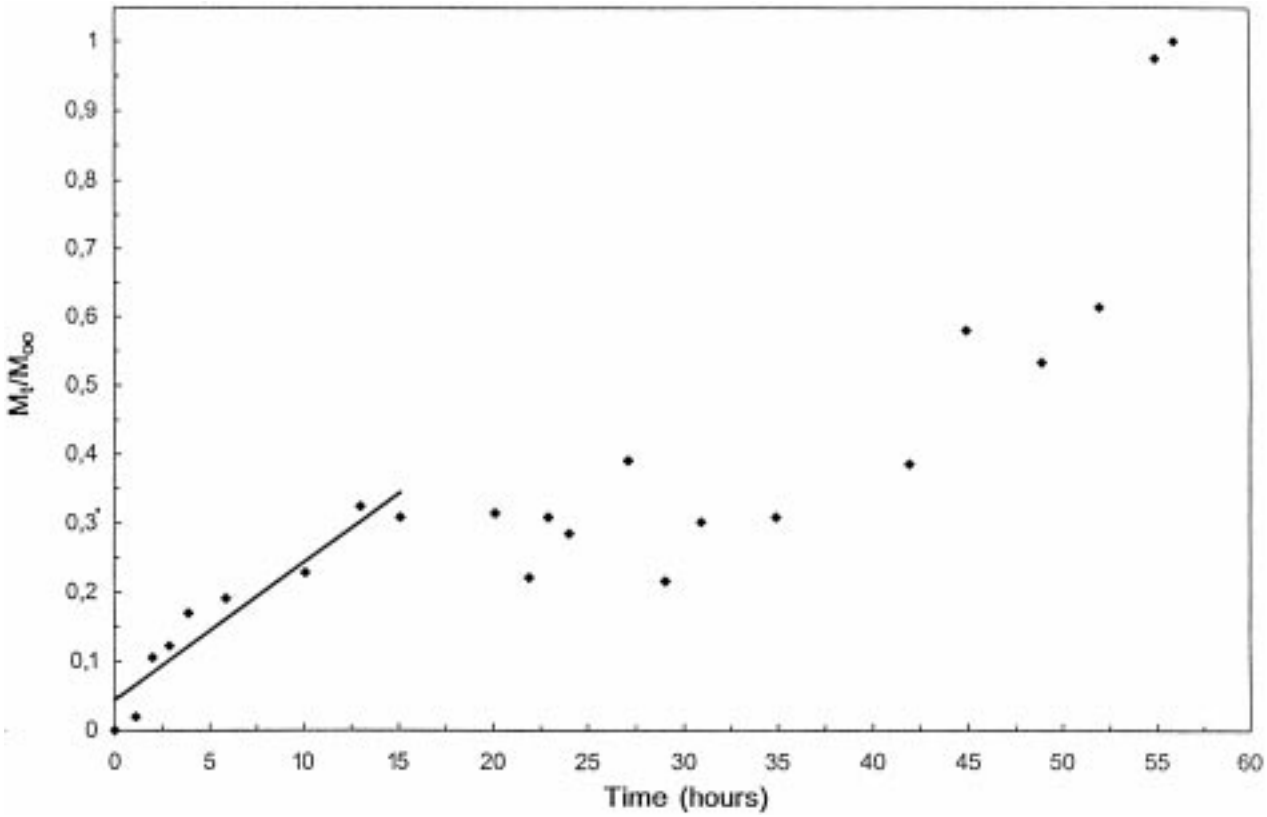

Figure 5 Release from poly(D,L-Lactide) $M_v = 22\,000$, loaded with 1% salicylic acid, in buffer solution.

Therefore, the higher concentration of SA can probably accelerate degradation and disturb a constant release rate.

5. Conclusions

From the above study the following conclusion can be drawn. Poly(D,L-Lactide) synthesized from the di-lactide monomer by ring opening polymerization technique can give products with various M_v, suitable for use in the controlled release of drugs. The low M_v materials degrade fast and this influences their swelling properties. Drug delivery seems to be linear with time for release up to 70% of the total amount of salicylic acid. On the other hand, the high M_v product is more stable to

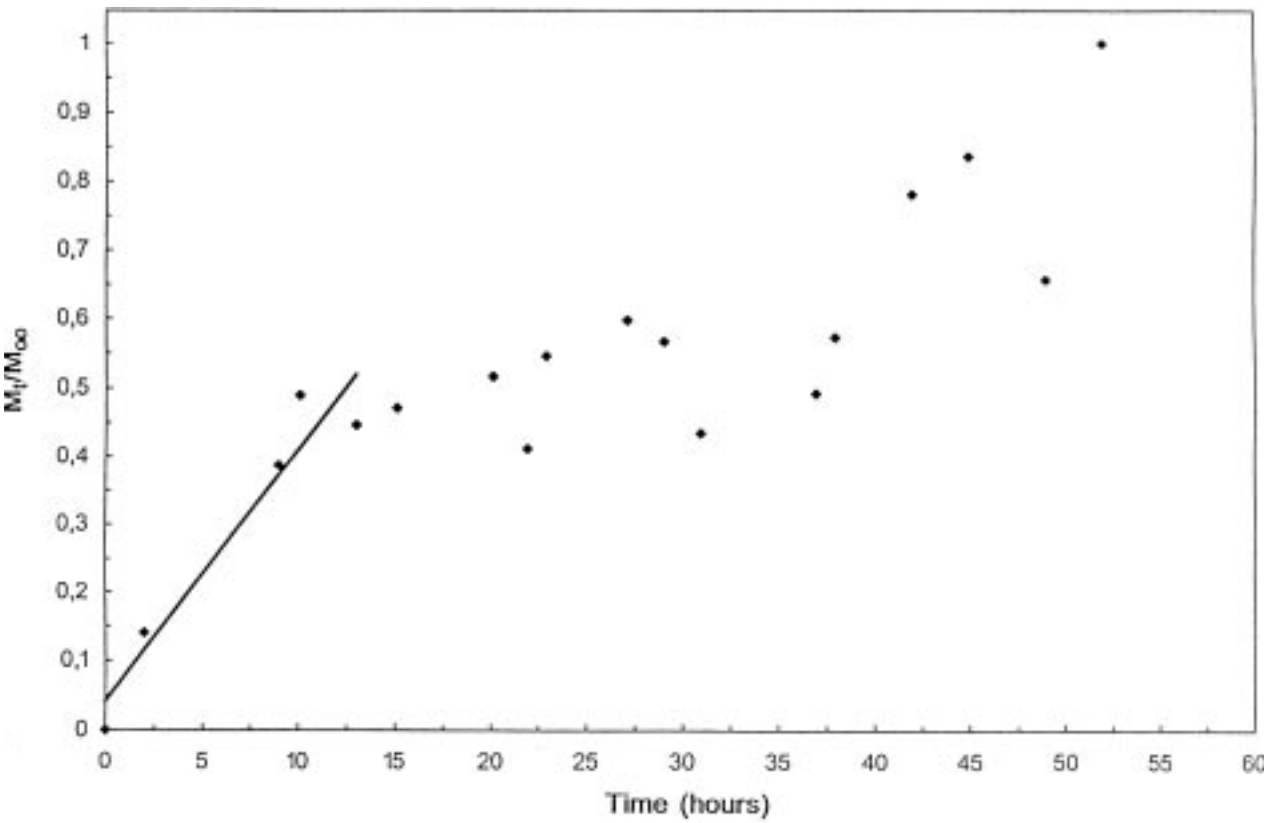

Figure 6 Release from poly(D,L-Lactide) $M_v = 2000$, loaded with 5% salicylic acid, in buffer solution.

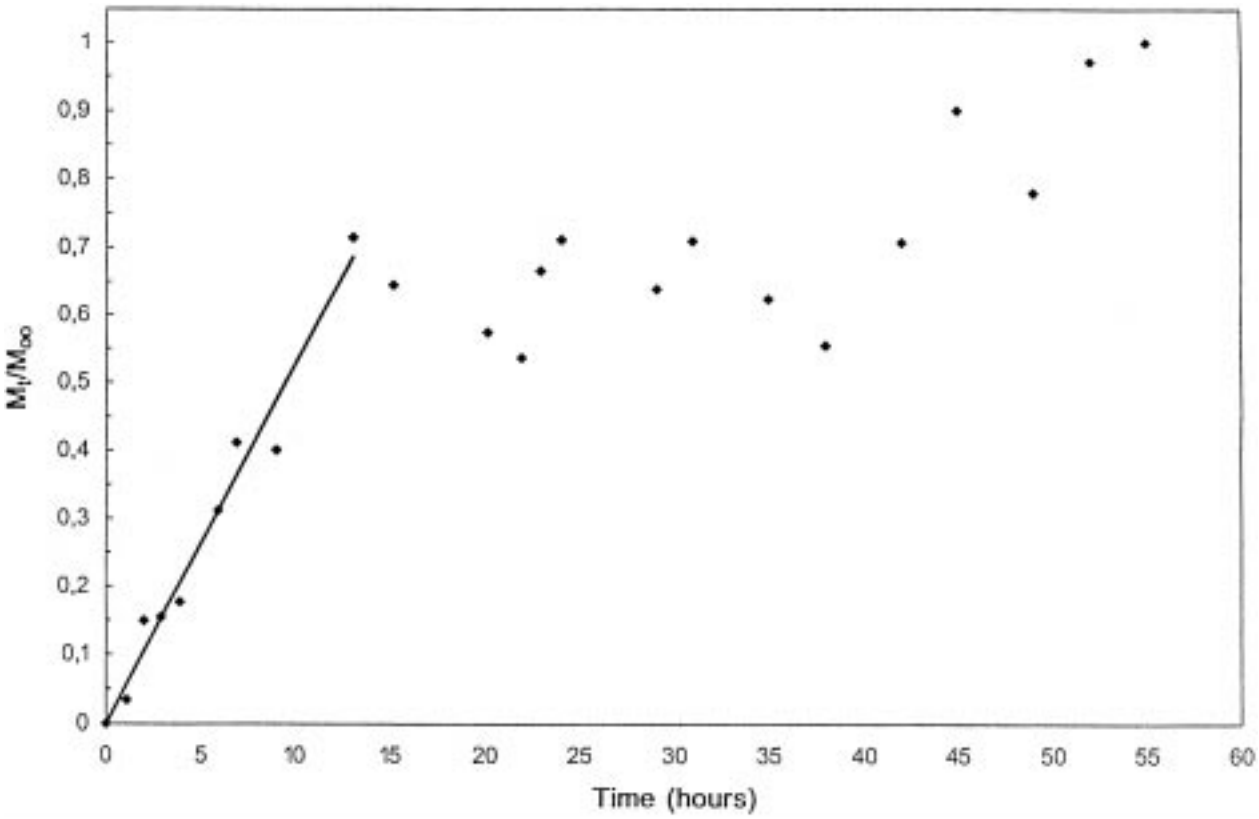

Figure 7 Release from poly(D,L-Lactide) $M_v = 2000$, loaded with 10% salicylic acid, in buffer solution.

biodegradation, its swelling fits better to Fickian behavior but the release of salicylic acid from its matrix tends to display linear dependence on the time only for high drug loadings.

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, *Pharmaceutical Research* **9** (1992) 200.
4. B. ELING, S. GOGOLEWSKI and A. J. PENNINGS, *Polymer* **23** (1982) 1587.
5. P. GANGADHARAM, D. ASHTEKAR, D. FAPHI and D. WISE, *Tubercle* **72** (1991) 115.
6. A. G. ANDREOPOULOS, *Journal of Biomaterials Applications* **10** (1995) 163.
7. D. WISE, G. MCCORMICK, G. WILLET, L. ANDERSON and J. HOWES, *J. Pharm. Pharmac.* **30** (1978) 686.
8. N. AMMOURY, H. FESSI, J. DEVISSAQUET, M. DUBRASQET and S. BENITA, *Pharm. Res.* **8** (1991) 101.
9. T. ISCHIHARA, K. SAKAMOTO, K. MORI and M. AKADI, *Cancer Research* **49** (1989) 4357.
10. O. IKE, Y. SHIMIZU, Y. IKADA, S. WATANABE, T. NATSUME, R. WADA, S. H. HYON and S. HITOMI, *Biomaterials* **12** (1991) 757.
11. P. BOTTENBERG, C. DEMUYNCK, S. BOUCKAERT, D. COOMANS, D. SLOP and J. P. REMON, *Proceed. Intern. Control. Res. Biaoct. Mater.* **18** (1991) 631.
12. J. W. LEENSLAG and A. J. PENNINGS, *Polym. Comm.* **28** (1987) 92.
13. H. R. KRICHELDORF, I. KREISER-SAUNDERS and C. BOETTCHER, *Polymer* **36** (1995) 1253.
14. J. W. LEENSLAG and A. J. PENNINGS, *Makromol. Chem.* **188** (1987) 1809.
15. J. W. LEENSLAG, A. J. PENNINGS, R. R. M. BOS, F. R. ROZEMA and G. BOERING, *Biomaterials* **8** (1987) 311.
16. O. PHILAJAMAKI, E. BOSTAMAN, P. HIRVENSALO, P. TORMALA and P. ROKKANEN, *J. Bone Joint Surg. [Br]* **74-B** (1992) 853.
17. P. P. CASTELEYN, F. HANDELBERG and P. HAENTJENS, *ibid.* **74-B** (1992) 858.
18. R. K. FRASER and W. G. COLE, *ibid.* **74-B** (1992) 929.
19. M. J. MANNINEN, *J. Mater. Sci.: Mater. Med.* **4** (1993) 179.
20. M. J. MANNINEN and T. POHJONEN, *Biomaterials* **14** (1993) 305.
21. M. J. MANNINEN, U. PAIVARINTA, H. PATIALA, P. ROKKANEN, R. TAURIO, R. M. TAMMINMAKI and P. TORMALA, *J. Mater. Sci.: Mater. Med.* **3** (1992) 245.
22. A. G. ANDREOPOULOS, E. C. HATZI and M. DOXASTAKIS, *ibid.* **10** (1999) 29.
23. E. C. HATZI, Ph.D Thesis, Unpublished Data, National Technical University of Athens, Chemical Engineering Department. Athens, 1997.
24. J. MAUDUIT, N. BUKH and M. VERT, *J. Contr. Rel.* **23** (1993) 209.
25. M. VERT, G. SCHWARCH and J. COUDANE, *J. Macromol. Sci., Pure Appl. Chem.* **A32(4)** (1995) 787.
26. A. G. ANDREOPOULOS, *Clinical Materials* **15** (1994) 89.
27. A. G. ANDREOPOULOS, T. KORAKIS, E. DOUNIS, K. KANELLAKOPOULOU, A. ANASTASIADIS and P. TZIVELEKIS, *J. Biomater. Appl.* **10** (1996) 338.
28. A. G. ANDREOPOULOS and M. PLYTARIA, *ibid.* **12** (1998) 258.
29. J. CRANK and G. S. PARK, ''Diffusion in Polymers'', (Academic Press, London 1968) p. 281.

Received 16 February
and accepted 12 April 2000