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Preparation and characterization of biodegradable poly(L-lactic acid) gentamicin delivery systems

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Summary

In the last two decades, localized antibiotic therapy has emerged as an important approach to treating orthopedic infections. This paper describes the preparation and in vitro evaluation of biodegradable, poly(L-lactic acid), implants for localized delivery of gentamicin sulfate for the treatment of osteomyelitis. Cylindrical, poly(L-lactic acid) implants containing gentamicin sulfate were obtained by compression of microcapsules prepared by a nonsolvent-induced, coacervation process. Mean particle size distributions of the microcapsules, based on volume, ranged from 278 to 444 μm. The gentamicin sulfate loading of the microcapsules, after a methylene chloride-water extraction procedure, exceeded 95% of the theoretical value. In vitro dissolution studies on microcapsules and implants with drug loading varying from 5 to 67% w/w indicated that the rate of gentamicin sulfate released from both microcapsules and implants increased, while the dissolution half-life (T_{50}) decreased, exponentially, with an increase in drug loading. Profiles of amount of drug dissolved at different times followed a square-root-time relationship. All batches of microcapsules and implants released greater than 80% gentamicin sulfate within 3 weeks. In comparison, previous studies in this laboratory have indicated that conventional, nonbiodegradable polymethylmethacrylate implants, containing gentamicin or tobramycin, show incomplete and poorly controlled drug release during the same time period.

Introduction

Osteomyelitis is an inflammatory bone disease caused by microbial infection of the bone medullary cavity, cortex and/or periosteum. One of the most common causes of osteomyelitis is post-operative sepsis following orthopaedic procedures. Prolonged parenteral and oral antibiotic therapy for 4–6 weeks may be necessary for treatment (Waldvogel, 1988). Some disadvantages of prolonged parenteral therapy by intravenous or intramuscular antibiotic injections are the high cost of treatment, systemic toxicity and patient discomfort. Oral antibiotic delivery may also be associated with patient compliance problems. In addition, because osteomyelitis is often associated with bone destruction and limited vascularity at the infected site, systemic therapy may fail to produce therapeutic tissue levels. Therefore, localized delivery of an antibiotic to the infected

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site was introduced in the seventies to overcome the difficulties associated with parenteral and oral therapy.

Since 1973, spherical, nonbiodegradable polymethylmethacrylate (PMMA) bone cement implants containing antibiotics have been extensively used for treatment as well as prophylaxis of bone infections (Klemm, 1981). Localized antibiotic delivery is advantageous because relatively high, local, tissue, drug levels may be obtained without corresponding high, toxic, blood levels. As PMMA implants are commercially unavailable in the United States, they are extemporaneously prepared by surgeons for clinical use. Surgical removal of these implants, after the duration of the therapy, is recommended. However, previous studies in our laboratory, using tobramycin-impregnated PMMA implants have indicated incomplete and poorly controlled in vitro release of tobramycin from these conventional implants (Robinson and Sampath, 1989). Also, pharmacokinetic studies of gentamicin-impregnated acrylic cement in 10 patients undergoing total hip joint arthroplasties indicated that only 5.78% of the total quantity implanted was released over 15 days (Bunetel et al., 1989).

Biodegradable polymeric carriers, on the other hand, obviate the need for surgical removal at the end of therapy because they are hydrolyzed in the body to form products that are easily resorbed or eliminated. The lactide/glycolide polymers have been widely investigated as carriers as they have been shown not to cause adverse tissue reactions (Thies, 1981; Leung et al., 1987). These poly(hydroxy acids) degrade in the body to lactic or glycolic acids, which are normal products of carbohydrate metabolism. Also, the use of these polymers potentially affords greater flexibility in the design of the drug delivery system and superior control of drug release compared with PMMA implants. Microcapsules, films or implants can be fabricated using these polymers.

The purpose of this study was to develop and characterize biodegradable, poly(L-lactic acid) (PLA), drug delivery systems that provide local bactericidal concentrations of gentamicin sulfate (GS) for 2–3 weeks. Gentamicin was selected for the study because it is a broad-spectrum antibiotic that has been widely used in PMMA bone cement implants for the treatment of osteomyelitis (Wahlig et al., 1978). The specific aims of the study were to prepare PLA microcapsules and implants containing GS, and to characterize the in vitro dissolution kinetics of GS from microcapsules and implants.

Materials and Methods

Materials

GS (lot no. 9G6612) and PLA (Medisorb™ 100L; lot no. S9229L051) were purchased from Paddock Labs Inc., Minneapolis, MN, and DuPont Co., Wilmington, DE. Methylene chloride and hexane were obtained from Baxter Healthcare Corp., McGaw Park, IL, and isopropanol and *o*-phthaldialdehyde from Sigma Chemical Co., St. Louis, MO. Disodium phosphate and potassium dihydrogen phosphate were purchased from Aldrich Chemical Co., Milwaukee, WI, and Mallinckrodt Inc., Paris, KY.

Methods

Preparation of microcapsules

Microcapsules were prepared by nonsolvent-induced coacervation. A weighed quantity of PLA, usually 3–5 g, was dissolved in methylene chloride to give a 2.5% w/v solution. Using a magnetic stirrer which provided an agitation rate of approx. 500 rpm, a known quantity of GS based on the drug loading, was suspended in the solution. To induce coacervation, an excess of hexane, usually 200–250 ml, which is a nonsolvent for PLA, was added at 3 ml/min with continuous stirring. The coacervate droplets adhered to the suspended drug particles and coalesced around them to form polymeric microcapsules.

The microcapsules were allowed to harden for 2 h, then decanted and washed twice with 50-ml portions of hexane. After a final separation by decantation, the microcapsules were dried for 10–14 h at 35°C to form a free-flowing powder. The microcapsules were passed through 40 and

120 mesh sieves to obtain a size fraction of 125–450 μm which was used for all further studies.

Preparation of implants

Cylindrical implants (0.5 × 1.0 cm) were prepared by compressing 250 mg of microcapsules in a die and punch apparatus at a pressure of 1 metric ton applied using a Carver hydraulic press.

In vitro evaluation

Microcapsule particle size A Brinkmann Particle Size Analyzer 2010, which functions on the principle of laser light-scattering, was used to determine the number, area and volume particle size distributions of a representative unsieved microcapsule sample, containing 33% w/w drug loading, and all batches of the 125–450 μm sieve fractions of microcapsules containing varying drug loading. The appropriate lens and prism combination was selected to measure particles in the size range of 10–1200 μm. Microcapsules were suspended in Freon TF® contained in a 1 cm cuvette and stirred during the measurement period. The sample size was automatically selected by the instrument based on the number of particles required to generate a volume distribution with 95% confidence.

Assay of drug content Triplicate samples (50 mg) of GS microcapsules were placed in methylene chloride to dissolve the PLA coat, and the drug was extracted five times with 5–8 ml of distilled deionized water. The aqueous extracts were mixed and the volumes were adjusted to 100 ml. Aliquots were assayed for GS content as described below. Percent yields were calculated based on the theoretical yields.

Analysis of GS GS was determined spectrophotometrically after derivatization with *o*-phthaldialdehyde (Sampath and Robinson, 1990).

In vitro dissolution Dissolution kinetics of GS (aqueous solubility > 1 g/l; Rosenkrantz et al., 1980) from each batch of microcapsules and compressed implants were studied in triplicate under sink conditions. Microcapsules (250 mg) or one implant were placed in a screw-capped bottle containing 100 ml of 0.07 M phosphate buffer, pH 7.4. Each bottle was agitated at 50 ± 2 rpm in a horizontally shaking water bath maintained at 37 ± 1°C. Samples were withdrawn at varying time intervals for a duration of 3 weeks, and the amount of GS released determined spectrophotometrically as described previously. Equal volumes of fresh phosphate buffer were added to replace aliquots removed for the assays.

Effect of drug loading The influence of drug loading, i.e., the drug to polymer ratio, on gentamicin release from microcapsules and implants was evaluated by studying the in vitro release characteristics of six different batches of drug delivery systems containing 5, 10, 20, 33, 50, and 67% w/w GS.

Data treatment After correcting for dilution of media, the in vitro release profiles of implants were fitted to

(a) first-order, kinetic relationships as proposed by Wagner (1969) to describe drug release from controlled-release formulations.

(b) Square-root-time plots of the type:

$$M_t/M_\infty = K_H t^{1/2}$$

where M_t is the amount of GS released at time t, M_∞ represents the amount of GS present initially and K_H is the rate constant for the corresponding best-fit line. The above relationship is similar to the expression developed by Higuchi (1963) for diffusion of a solute from porous matrix systems.

Scanning electron microscopy (SEM) A Philips Model 515 Scanning Electron Microscope was used to observe the morphology of implants containing 33% w/w GS before and after in vitro dissolution.

Results and Discussion

Preparation of microcapsules

Most published procedures for microencapsulation with the lactide/glycolide polymers employ solvent evaporation techniques that have been developed for water-insoluble drugs (Splenhauer et al., 1986; Bodmeier and McGinity, 1987). These procedures require the formation of emulsions and are inefficient for encapsulating water-soluble drugs which can partition preferentially into the aqueous phase (Lewis, 1990). Phase separa-

tion methods using organic solvents in which these drugs are insoluble, would, on the other hand, facilitate their encapsulation. A phase separation procedure employing a solvent-nonsolvent combination of methylene chloride and mineral oil has been reported for poly(DL-lactide) by Leelarasamee et al. (1988). The use of hexane as a nonsolvent, however, permits easier washing and drying of microcapsules as it is more volatile than mineral oil.

Implant weight variation

Weight variation studies on implants indicated that the mean weights of implants were 250.8–252.7 mg. The percent coefficient of variation for each batch was less than 0.05%.

Particle size

The particle size distribution, based on particle number, for the representative unsieved microcapsules indicated that the mean diameter was 14.8 μm. A volume-based size distribution indicated a log-normal distribution with the mean at 343 μm. The size distributions of the 40–120 mesh sieve fraction for all batches were similar to the unsieved sample. Table 1 summarizes the number and volume means for the various batches

TABLE 1

Sample means for number, area and volume distributions (Martin et al., 1983) for various batches of gentamicin sulfate microcapsules

Sample	Distribution means (μm)		
	Number	Area	Volume
Expression used [a]	ΣxN $/\Sigma N$	Σx^3N $/\Sigma x^2N$	Σx^4N $/\Sigma x^3N$
Unsieved sample	14.8	99.9	343
Sieved samples			
Drug loading (%)			
5	16.0	174	433
10	16.2	169	388
20	16.4	209	444
33	19.4	251	404
50	14.2	94	284
67	16.8	130	278

[a] N, number of particles; x, particle size.

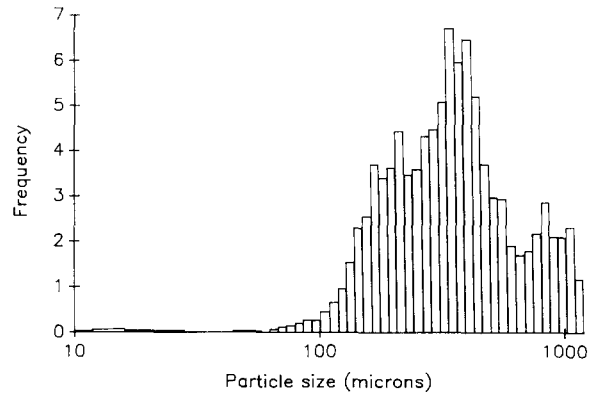

Fig. 1. Particle volume distribution of gentamicin sulfate microcapsules.

as well as the mathematical expressions used in their determination. The means of the number and the volume distributions ranged from 14.2 to 19.4 μm and 278 to 444 μm, respectively. In general, batches with higher drug loading had a lower volume-moment mean. A typical volume distribution of a sample containing 33% w/w GS is shown in Fig. 1. The number and volume distributions of the sample are shown in Table 2. The number distribution data indicates that more than 92% of the particles had diameters less than 24 μm. The volume distribution data showed that about 59–78% of the population had diameters in the range of 100–500 μm. The difference between the number and volume means indicates that during the particle size measurement proc-

TABLE 2

Typical particle size distribution of microcapsules with 33% w/w gentamicin sulfate

Distribution	Mean (μm)	S.D. (μm)	Range (μm)	Percent
Number	16.1	16.3	8– 16	69.8
			16– 24	22.5
			24– 200	7.5
Area	165.9	188.7	8– 100	48.7
			100– 500	44.5
			500–1200	6.8
Volume	380.6	238.9	8– 100	7.7
			100– 500	64.4
			500–1200	27.9

TABLE 3

Assay of gentamicin sulfate content of microcapsules

Batch	Theoretical (% w/w)	Experimental (% w/w)	
		Mean ($n = 3$)	S.D.
1	5.00	6.16	1.30
2	10.00	10.86	3.50
3	20.00	19.06	4.72
4	33.33	35.46	1.92
5	50.00	54.92	6.80
6	66.67	65.10	6.73

ess, aggregates may break down to yield a large number of particles with a small particle size. Alternatively, the fines could be due to hardened coacervate droplets that were not removed during the sieving process. The volume distribution data, which more accurately reflects the particle size of microcapsules, indicates that smaller particles did not significantly contribute to total particle volume.

Assay of drug content

Table 3 summarizes the results of the assay of drug content for different batches of microcapsules. The percent yield was greater than 95% for all batches. This indicates that little drug was lost during the microencapsulation process. The low coefficients of variation for batches with 5–33% w/w drug loading indicate a homogeneous distribution of the drug. The greater variation with microcapsules containing 50 and 67% w/w GS is possibly due to a higher percentage of unencapsulated drug, which could have resulted from increased drug loading.

In vitro dissolution

Release profiles of uncompressed microcapsules containing 5, 10 and 33% w/w GS are shown in Fig. 2. The release profiles of uncompressed microcapsules containing 50 and 67% w/w GS are similar to that of microcapsules containing 33% w/w GS while microcapsules with 20% w/w drug had a release profile similar to those with 10% w/w loading. An initial burst release of 25–35% of GS was seen for the various

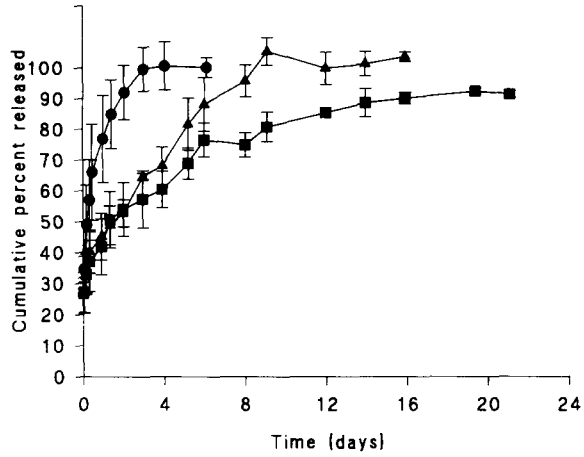

Fig. 2. Gentamicin sulfate release from poly(L-lactic acid) microcapsules. (■) 5%, (▲) 10%, (●) 33%.

batches which can be attributed to drug on the surface of the microcapsules or unencapsulated drug. Complete drug release occurred within 3 weeks. Microcapsules with higher drug loading, i.e., 33% w/w drug or greater, showed essentially complete release of GS in 3 days, while those containing 20% w/w drug or less showed a more prolonged release.

The release of GS from cylindrical implants was more prolonged and less variable than from microcapsules. This can be explained by the smaller and less variable surface area of the implant as compared to uncompressed microcapsules. In vitro dissolution studies indicated that implants with 5, 10 and 20% w/w drug showed small initial burst releases of GS of less than 5% (Fig. 3). Implants prepared from microcapsules with 33, 50 and 67% w/w drug showed initial burst releases of 13, 30 and 44%. GS dissolution from implants containing 33% w/w drug or greater was complete in 4 days; implants with 5, 10 and 20% w/w drug showed prolonged release for 12–18 days. As in the case of microcapsules, all batches of implants showed nearly complete release of GS in the duration of the experiment. No significant erosion of the implant matrix occurred during the study.

In comparison, previous studies in this laboratory using the conventional, spherical, PMMA implants indicated that tobramycin release from

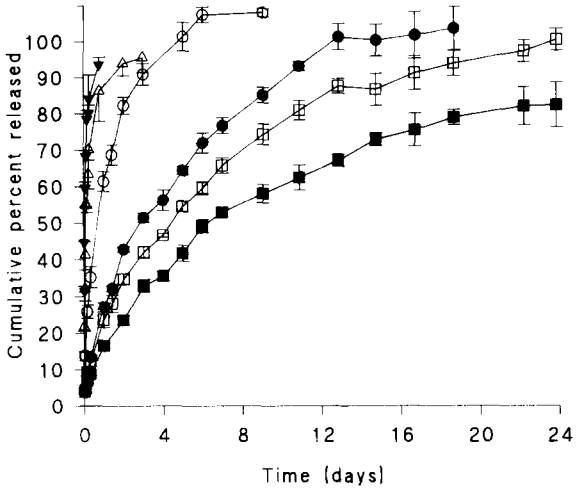

Fig. 3. Gentamicin sulfate release from poly(L-lactic acid) implants. (■) 5%, (□) 10%, (●) 20%, (○) 33%, (△) 50%, (▼) 67%.

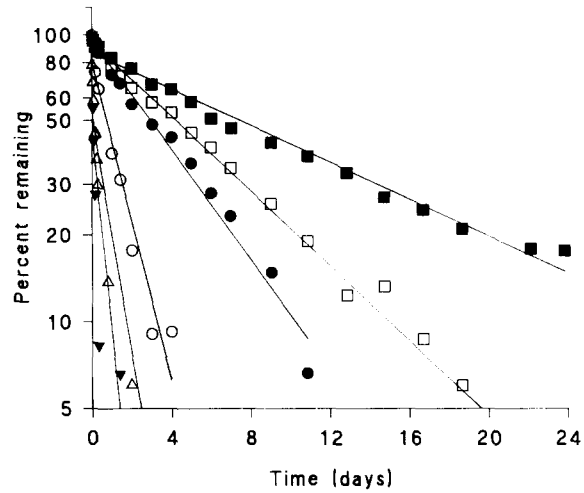

Fig. 4. Log (percent remaining) vs. time profiles of gentamicin sulfate release from poly(L-lactic acid) implants. (■) 5%, (□) 10%, (●) 20%, (○) 33%, (△) 50%, (▼) 67%.

implants with similar drug loading is incomplete (Robinson and Sampath, 1989). Only 20% of the tobramycin initially present was released from a single implant in 3 weeks. Also, the release from PMMA implants was poorly controlled, showing a significant burst release (about 80% of the total amount released) in the first 24 h, followed by slow release of the remaining amount over 3 weeks. Studies with PMMA cylinders (0.5×1.0 cm) containing gentamicin and tobramycin (Weston et al., 1991) also showed incomplete and poorly controlled release.

First-order plots and square-root-time plots of the release profiles are shown in Figs 4 and 5. The coefficients of determination, r^2 values, for the best-fit lines and the rate constants (calculated from the slopes of the best-fit lines) are listed in Table 4. The square-root-time fits showed higher r^2 values than the first-order plots in all cases. These square-root-time plots indicate that release of GS from PLA implants is diffusion-controlled with the drug leaving the matrix through pores and channels formed by entry of the dissolution medium. Graphs of log percent released vs log t for all drug loadings are shown in Fig. 6. The slopes of the best-fit lines ranged from 0.43 to 0.59, with r^2 greater than 0.98, indicating diffusion-based release which predicts a theoretical value of 0.5 (Peppas, 1985).

The T_{50}, i.e., time taken for 50% of the avail-

TABLE 4

Release kinetics of gentamicin sulfate from poly(L-lactic acid) implants

Drug loading (% w/w)	First-order data fits		Square-root-time data fits		T_{50} (days)
	Rate constant, k ($days^{-1}$)	r^2	Rate constant, K ($days^{-1/2}$)	r^2	
5	0.074	0.984	19.10	0.995	7.12
10	0.150	0.995	24.95	0.999	4.23
20	0.220	0.980	29.90	0.997	3.08
33	0.636	0.950	56.58	0.998	0.70
50	1.796	0.914	120.6	0.970	0.12
67	1.568	0.618	173.6	0.994	0.06

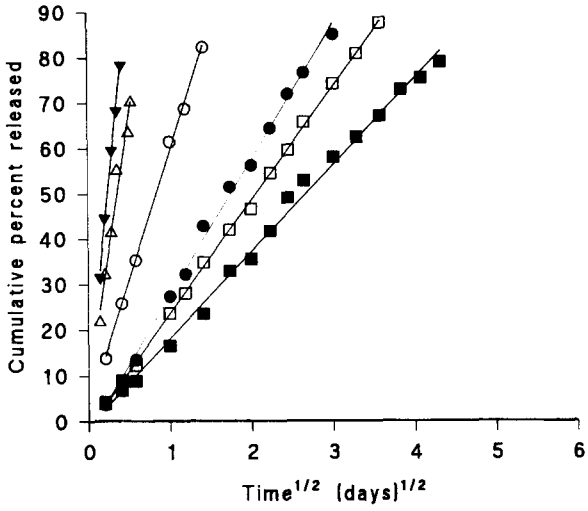

Fig. 5. Gentamicin sulfate release from poly(L-lactic acid) implants: square-root-time plots. (■) 5%, (□) 10%, (●) 20%, (○) 33%, (△) 50%, (▼) 67%.

able GS to dissolve, calculated from the square-root-time plots, increased from 0.05 to 7.3 days with a decrease in drug loading. Implants with more than 33% w/w drug had dissolution half-lives of less than a day. The data indicated that the rate of release of gentamicin increased with an increase in drug loading. Fig. 7 indicates that a plot of $\log(T_{50})$ vs the drug loading (expressed as mg of GS per implant) yields a linear relationship

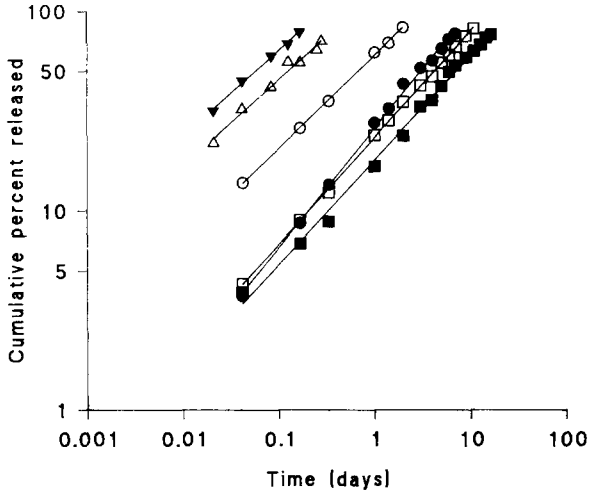

Fig. 6. Gentamicin sulfate release from poly(L-lactic acid) implants: log-log plots. (■) 5%, (□) 10%, (●) 20%, (○) 33%, (△) 50%, (▼) 67%.

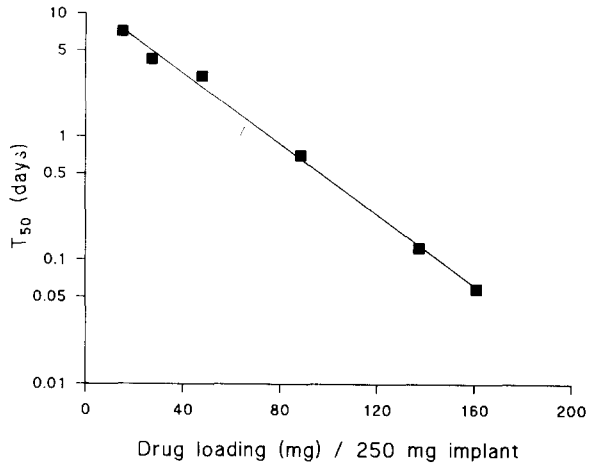

Fig. 7. The relationship between dissolution half-life and drug loading.

($r^2 = 0.996$) which can be described by the equation:

$$\log(T_{50}) = -0.014(\text{drug loading}) + 1.088.$$

Thus, the T_{50} decreases exponentially with an increase in drug loading. A plot of release rate constant, K, vs drug loading indicated a positive deviation from linearity over the range of drug loading used in the study. However, a plot of log K vs drug loading was linear. A linear relationship has been proposed by Higuchi (1963) for drug release from a granular matrix. Other investigators have observed positive deviations from linearity (Borodkin and Tucker, 1974; Samuelov et al., 1979; Bodmeier and Paeratakul, 1989). For example, Borodkin and Tucker (1974) observed that increasing the proportion of hydroxypropyl cellulose in a hydroxypropyl cellulose-polyvinyl acetate film resulted in an exponential increase in the release rate. Samuelov et al. (1979) proposed that at higher drug loadings, drug is leached rapidly from the implant resulting in an increase in pore formation, with corresponding increase in porosity and a decrease in tortuosity. This leaching of the drug results in an increase in the surface area exposed to the dissolution medium, with a corresponding increase in K and decrease in T_{50}.

Fig. 8. Surface of poly(L-lactic acid)-gentamicin sulfate (33% w/w) implants before dissolution, magnification 156 ×.

The relationship between T_{50} and drug loading is based on values of drug loading ranging from 5 to 67% w/w GS and can be used to determine the drug content of an implant designed to have a particular value of T_{50}. Thus, implants with varying durations of GS release can be manufactured by selecting the appropriate levels of drug loading. However, the value of the intercept indicates that decreasing drug loading cannot prolong the dissolution half-life beyond 11 days and other methods, such as increasing compression pressure coating the implant or using a polymer with a larger molecular weight, may be required to prolong the release.

SEM studies

SEM of implants with 33% w/w drug loading before dissolution (Fig. 8) indicate a relatively smooth surface with very few pores. However, after dissolution (Fig. 9) the surface showed an increase in the number of pores and channels. SEM studies confirm that an increasing number of pores and channels were formed during dissolution by the entry of dissolution medium.

Conclusions

In comparison with PMMA implants, PLA drug delivery systems show an improved extent of release; therefore, they may be an economical and effective treatment for osteomyelitis. The release of GS from PLA implants followed a square-root-time relationship indicative of a diffusional release mechanism. Also, release can be quantitatively related to drug loading, thus facili-

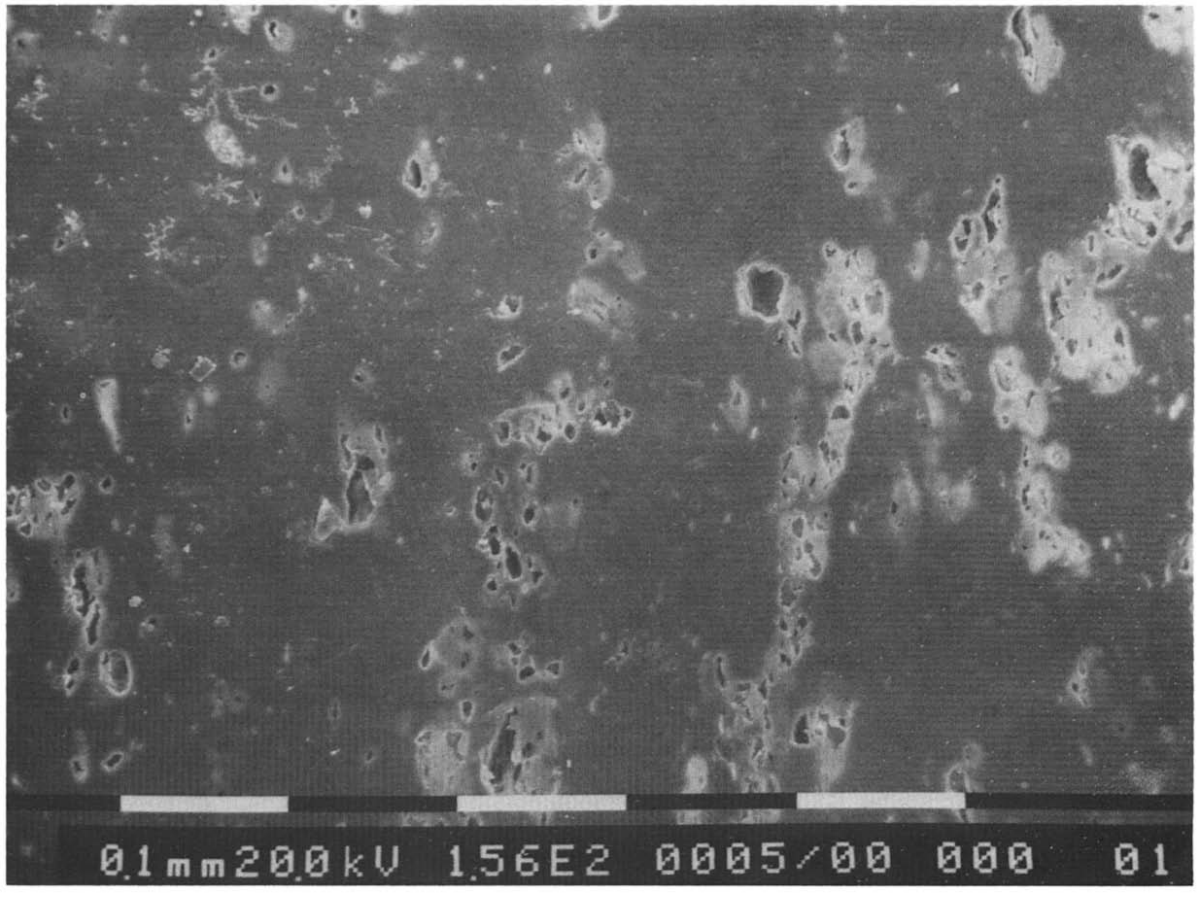

Fig. 9. Surface of poly(L-lactic acid)-gentamicin sulfate (33% w/w) implants after dissolution, magnification 156 ×.

tating the design of implants with desired durations of drug release.

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