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Biodegradable Controlled Antibiotic Release Devices for Osteomyelitis: Optimization of Release Properties

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Abstract—Controlled antibiotic release films, melt-extruded cylinders, and suspension-extruded/coated cylinders were manufactured from biodegradable poly(D,L-lactide) (PDLLA) and poly(D,L-lactide-co-ϵ-caprolactone). These devices have potential application in the treatment of osteomyelitis. The in-vitro release properties of the devices were examined with drug loadings varying from 16 to 50%. Gentamicin sulphate films and melt-extruded gentamicin/PDLLA cylinders demonstrated a large initial burst and incomplete release. The films and melt-extruded cylinders made from poly(D,L-lactide-co-ϵ-caprolactone), low mol. wt poly(D,L-lactide), and a mixture of D,L-lactic acid oligomer and high mol. wt poly(D,L-lactide), did not remain intact during the entire release period. While this is undesirable, these materials do have the advantage of not requiring a processing temperature of greater than 110°C. Antibiotic release from high mol. wt PDLLA-coated gentamicin/PDLLA cylinders, with 40 and 50% loading, was very rapid. The antibiotic could only diffuse out through the open ends of the cylinder. Coated gentamicin sulphate cylinders with 20 and 30% drug loading gave the most promising properties in terms of a small initial burst, and a gradual and sustained release. The release rate and duration from the coated cylinders could be adjusted by cutting the cylinder into different lengths; the time required for 90% of the entrapped gentamicin to be released into water from 30% loaded PDLLA-coated cylinders 0·2, 0·4, 0·7 and 1 cm in length was 1000, 1700, 2300, and 2800 h, respectively. This offers a convenient method to adjust the release to meet the specific antibiotic requirement of different patients. Cephazolin and benzylpenicillin were found to be unsuitable for sustained release longer than 300 h due to the hydrolytic instability of the drugs in water.

Bone infection (osteomyelitis) in orthopaedic bone surgery is very hard to treat. Local antibiotic administration, which should last for 4–6 weeks, is normally considered the best way to treat this condition (Schlossberg 1988; Coombs & Fitzgerald 1989). Gentamicin poly(methyl methacrylate) (PMMA) beads have been employed clinically to prevent or treat osteomyelitis since the 1970s (Trippel 1986). However, since PMMA is a non-biodegradable material, secondary surgery is required to remove the beads after gentamicin has been released. Several biodegradable controlled antibiotic-release devices, such as dideoxykanamycin hydroxyapatite/poly(lactic acid) cylinders (Ikada et al 1985), ampicillin poly(D,L-lactide-co-glycolide) microcapsules (Setterstrom et al 1991), cefotiam hydroxyapatite beads (Yamamura et al 1992), and gentamicin poly(L-lactic acid) microcapsules and cylinders (Sampath et al 1992) have recently been developed (Ikada et al 1985; Setterstrom et al 1985, 1991; Firsov et al 1987; Wei et al 1990; Sampath et al 1992; Shinto et al 1992; Yamamura et al 1992; Yu et al 1992). However, the release properties of these devices were not found to be satisfactory primarily due to poor design and manufacturing. For example, in in-vitro studies more than 40% of entrapped gentamicin was released from poly(L-lactic acid) microcapsules in the first few hours. The release from uncoated poly(L-lactic acid) cylinders was barely longer than three weeks (Sampath et al 1992).

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For a water-soluble drug in a brittle hydrophobic polylactide matrix, the release mechanisms are controlled by channel diffusion, osmotic pressure and polymer degradation (Zhang et al 1993a). Firstly, when drug loading is low, drug particles will be isolated in the polymer matrix. These particles will not be able to permeate through the polymer at a practically useful rate due to the very low permeability of water-soluble drugs in a hydrophobic polymer. With an increase in drug loading, some drug particles will be connected together to form channels leading to the surface of the device. These drug particles will be releasable by channel diffusion (Siegel & Langer 1990). Secondly, if the polymer matrix surrounding the isolated drug particles remains intact during release, drug will not be released from these clusters. However, water will be taken up by a water-soluble drug with high osmotic pressure through the polymer, thus causing swelling of the drug particle. The polymer matrix may break under this swelling to form openings for drug release. Finally, when the polymer mol. wt decreases sufficiently, loss of polymer begins. The drug will then be released along with this polymer loss.

The major aim in this paper was the development of a matrix type biodegradable antibiotic-release device with controllable release characteristics. The release profile should have an initial high release rate, to accommodate the possibility of infection just after an operation, followed by 4–6 weeks of more or less constant release. Biocompatible and biodegradable polymers, such as poly(D,L-lactide) or its copolymer with ϵ-caprolactone, were used to make the devices, such as cylinders and films, containing cephazolin, and benzylpenicillin.

Materials and Methods

Materials

o-Phthaldialdehyde and sodium borate were purchased from Aldrich Chemical Co., Milwaukee, WI. Benzylpenicillin (benzylpenicillin sodium salt) was obtained from Sigma Chemical Co., St Louis, MO. 2-Mercaptalmethanol and potassium chloride were purchased from BDH Chemicals Canada Ltd, Toronto, Canada. Cephazolin sodium was purchased from SmithKline Beecham Inc., Oakville, Ontario. Gentamicin sulphate powder was a gift from Schering Canada Inc., Pointe Claire, Quebec. Particle size distributions were measured with a Java (Jandel Scientific) image analysis system.

High mol. wt poly(D,L-lactide) (PDLLA), poly(D,L-lactide-co-ϵ-caprolactone (P(DLLA-co-CL)), low mol. wt poly(D,L-lactic acid), D,L-lactic acid (DLLA) oligomer, and mixture of high mol. wt PDLLA and DLLA oligomer were synthesized in our laboratory (Zhang et al 1993b).

Manufacture of controlled-release devices

Three types of controlled-release devices were manufactured: melt-pressed films, melt-extruded cylinders, and suspension-extruded/coated cylinders.

Melt-pressed films

A PDLLA or P(DLLA-co-CL) acetone solution was mixed with antibiotic powder and then thoroughly dried to form a uniform drug-polymer mixture. This mixture was hot-pressed between two polytetrafluoroethylene plates for 5 min at 70–110°C at 500 lb in^{-2}. The drug loadings examined were 16, 32 and 42·8%.

Melt-extruded cylinders. Sometimes polymers with low melt processing temperatures (Sampath & Robinson 1990) are required for making controlled-release devices to prevent drug decomposition. Polymers that can be employed in these applications include low mol. wt poly(D,L-lactic acid) (mol wt. 4800 Da), high mol. wt PDLLA containing D,L-lactic acid oligomer, and P(DLLA-co-CL). Polymer drug-mixtures were made in the same way as described in the previous section. The drug-polymer mixture was then extruded through a syringe at 70–100°C. The drug loadings tested were 16, 30, 40 and 50%.

Suspension-extruded/coated cylinders. PDLLA (viscosity average mol. wt $3{\cdot}26 \times 10^4$ Da) was dissolved in acetone to form a viscous 50% polymer solution. Antibiotic powder was mixed with the polymer solution to form a viscous suspension. This suspension was extruded with a syringe to give a cylindrical core about 2 mm in diameter. The cylinder core was air dried overnight and then coated with pure PDLLA by running the cylinder core through a pipette tip containing a pure PDLLA (10%) acetone solution (mol wt. 55×10^4 Da) (Zhang et al 1993a). The drug loading of the cylinder core was varied from 20 to 50%. The coated cylinders were completely dried in-vacuo and cut into different lengths (ranging from 0·2 to 4 cm) for release studies.

Antibiotic release studies

The cylinders or films were placed into distilled water or potassium chloride solutions, which were agitated in a horizontally-shaking water-bath maintained at 37°C. Drug concentrations were determined with a UV/vis scanning spectrophotometer (Philips PU 8720). The elution solutions were replaced at every measurement, which ranged from a few hours to one week. Sufficient measuring times were employed to approach the sink condition (i.e. a condition where the drug concentration in the eluent can be treated as zero compared with drug solubility). Sampath & Robinson's (1990) procedure for analysing gentamicin sulphate was followed with a slight modification. *o*-Phthaldialdehyde reagent was formulated by adding 2·5 g *o*-phthaldialdehyde, 62·5 mL methanol and 3 mL 2-mercaptalmethanol to 560 mL 0·04 M sodium borate in distilled water solution (Jones et al 1981). The reagent was stored in a brown bottle in a dark chamber and settled for at least 24 h before use. One millilitre gentamicin solution, 1 mL *iso*-propanol and 1 mL *o*-phthaldialdehyde reagent were reacted for 45 min at room temperature (20°C). The absorbance, which corresponds to the gentamicin concentration,

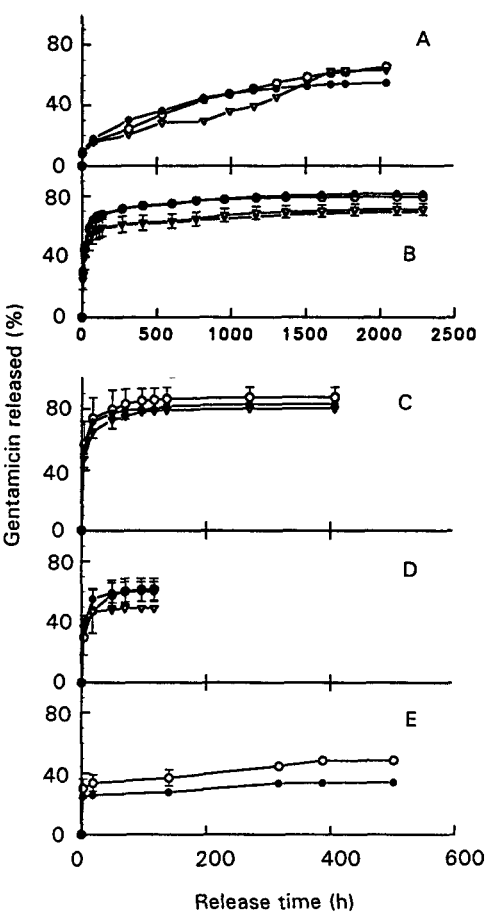

FIG. 1. Release of gentamicin sulphate from melt-pressed films into KCl solutions of varying concentration (0–30 g L^{-1}). A. In water, 15% loading. ● P(DLLA-co-CL), 15·9% CL; ▽ P(DLLA-co-CL), 31% CL; ○ PDLLA. B. PDLLA, 30% loading. KCl concn (g L^{-1}) ○ 0, ● 10, ▽ 20, ▼ 30. C. P(DLLA-co-CL), 15·9% CL, 42·8% loading. KCl concn (g L^{-1}) ○ 0, ● 10, ▽ 20. D. P(DLLA-co-CL), 31% CL, 30% loading. KCl concn (g L^{-1}) ○ 0, ● 10, ▽ 20, ▼ 30. E. P(DLLA-co-CL), 55% CL, 30% loading. KCl concn (g L^{-1}) ○ 0, ● 20. CL = caprolactone.

was then measured at 333 nm. The working range was 5–300 ppm. A calibration curve was made for each set of measurements. The calibration lines were the same within experimental error for at least 1000 h (correlation coefficient > 0.99; slope $0{\cdot}0112 \pm 0{\cdot}0004\ ppm^{-1}$; degrees of freedom 9), which indicated that the formulated *o*-phthaldialdehyde reagent was stable.

The method of Mays et al (1975) was employed to analyse the cephazolin concentration at a wavelength of 473 nm. Benzylpenicillin concentration was determined by the method of Bundgaard & Ilver (1972) at 325 nm. Both methods measured only intact cephazolin or benzylpenicillin.

The unreleasable drug fraction in the device was obtained by dissolving the cylinder or film in chloroform, and then extracting the chloroform solution with water. The drug concentration in the water extractant corresponded to the unreleasable drug in the device.

Results and Discussion

Gentamicin release from hot-pressed films

Large initial antibiotic bursts were observed for the polymer/gentamicin films with 30 and 42·8% loading. The initial burst was much smaller for 15% gentamicin-loaded films (Fig. 1). The initial burst was due to the dissolution or diffusion of drug particles attached or close to the film surface. The large initial bursts for the films with high drug loadings were obviously due to more drug clusters connected to the device surface. The large surface area of the films also enhanced the initial burst. The salt concentration of eluent did not affect the initial burst but decreased the releasable fraction. Since a concentrated salt solution has a higher osmotic pressure, the driving force (the osmotic pressure difference between drug and eluent) for water uptake by the antibiotic decreases. Therefore, the swelling of the isolated drug clusters, which causes deformation and finally fracture of the polymer, decreases. This results in less fracturing of the polymer and a lower releasable drug fraction. However, the salt concentration effect was not large since most of the drug was released in the initial burst. With an increasing caprolactone content in the polymer, the magnitude of the initial burst as well as the releasable drug fraction decreased. This can be explained by increasing polymer flexibility (for example, increasing elongation at tensile break), with increasing caprolactone content. More flexible polymers require a greater degree of swelling before the polymer can be broken. Furthermore, relaxation of the copolymer, with a high caprolactone content in water, tends to fill the channel that was originally available for drug release. After a period in water, the film with 31% caprolactone content and 15% drug loading became more homogenous than in the case of a pure PDLLA film with the same loading (i.e. no apparent pore structure was observed for the copolymer). An apparent pore structure was observed for the PDLLA film, which was not seen with the copolymer film. Polymer relaxation was also reflected by the dimension change of the film. For example, for the 30% gentamicin-loaded films after 502 h in eluents, with ϵ-caprolactone contents of 0, 15·9, 31·0, and 55·0% in the polymer, the diameter changes were $0 \pm 1{\cdot}8, 2{\cdot}0 \pm 2{\cdot}4, 11{\cdot}0 \pm 6{\cdot}5$ and $-52 \pm 2.6\%$, respectively. Finally, flexible copolymer may entrap drug particles more easily under the same manufacturing conditions. These three reasons might account for the low initial burst and low releasable fraction from the more flexible copolymers.

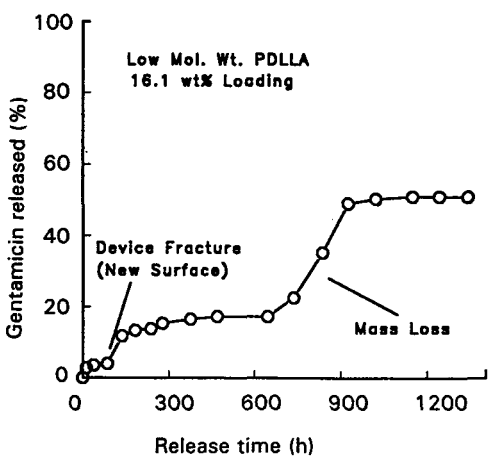

FIG. 2. Release of gentamicin sulphate from melt-extruded cylinders of low mol. wt PDLLA. The final releasable fraction was much less than one might expect due to material loss during eluent replacement and washing.

Release of gentamicin from melt-extruded cylinders

To reduce the initial burst in the film device, a melt-extrusion method for making cylinders was examined, since a cylinder has a lower surface/weight ratio than a film. The low mol. wt poly(D,L-lactic acid) (mol wt. 4800 Da) gentamicin cylinder was very brittle and could be easily broken at room temperature (25°C). However, the cylinder became soft and flat at 37°C after incubating in distilled water for a few hours. The release from low drug-loaded (16·4 wt%) devices is shown in Fig. 2. After an initial burst during the first few hours, very little gentamicin was released in the following 700 h. The release rate then dramatically increased to give a more or less constant release rate over a 200 h period. Rapid mass loss of the device occurred from 700 to 900 h. Channel diffusion and osmotic pressure were not considered important in this case due to the low drug loading and the high flexibility of the polymer (not fracturable under osmotic pressure) in water. With this system, antibiotic release was degradation controlled.

It was hoped that the undesirable material properties (i.e. shape loss in water at 37°C) of low mol. wt poly(D,L-lactic) acid could be overcome by using a mixture of high mol. wt poly(D,L-lactide) and DLLA oligomer. The cylindrical shape remained intact during the release although there was swelling. The antibiotic release profile also consisted of three stages: an initial burst, slow release in the following 700 h, and a very fast constant release from 700 to 900 h (Fig. 3B). This was very similar to the release profile of the low mol. wt poly(D,L-lactic acid) cylinder (Fig. 2). The magnitude of the initial burst depended very much on the oligomer content; for example, 17% of the entrapped gentamicin was released in the initial burst when the oligomer content was 20% in the polymer, while 80% of the gentamicin was released at an oligomer content of 25%

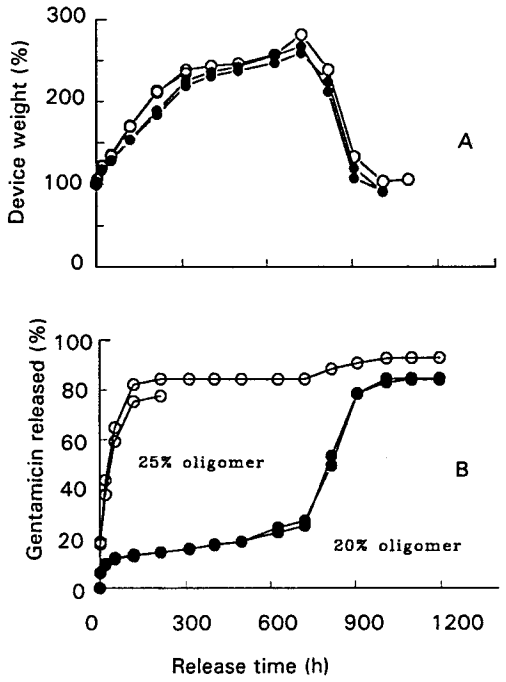

FIG. 3. A. Wet weight change of melt extruded gentamicin cylinders (30% loading) made from a mixture of high mol. wt PDLLA and DLLA oligomer. B. Gentamicin release behaviour from these devices.

(Fig. 3B). This extreme sensitiveness of release to oligomer content may be due to the fact that the DLLA oligomer was hydrophilic, so that its presence probably enhanced channel diffusion release.

The slow release which followed the initial burst might be due to drug release under osmotic pressure. The rapid constant release in the last stage corresponded to polymer mass loss. Indeed, the high constant release rate occurred at the same time as mass loss of the device (Fig. 3A). The device absorbed water quickly during the first 350 h and then absorption slowed during the next 350 h before rapid polymer mass loss was observed. It is very interesting to note that the lost polymer material was mainly from the cylinder core. A brittle cylindrical skin was left after 900 h, which corresponded to the end of the period of polymer-mass loss. Although the gentamicin contents in the two types of devices at the second release stage (slow release) were very different, no differences in water absorption behaviour and degradation behaviour were observed (Fig. 3A). Rapid core degradation might be due to the fact that more DLLA oligomer eluted from the outer part of the cylinder, while polymer degradation was catalysed by carboxylic groups in the DLLA oligomer remaining in the core (Pitt et al 1981; Li et al 1990).

Another type of melt-extruded cylinder was made from poly(D,L-lactide-co-ϵ-caprolactone) with 55% ϵ-caprolactone. At 30% gentamicin loading, the release mechanism was dominated by the effect of osmotic pressure (Fig. 4) since salt concentration in the eluent had a critical effect on the release, while at 40 and 50% gentamicin loading, the channel-diffusion mechanism dominated. No significant osmotic pressure effect was observed since the KCl concentration did not have an effect on the release pattern. The device's

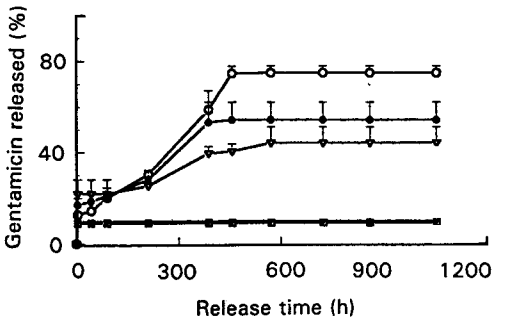

FIG. 4. Release of gentamicin sulphate from melt extruded gentamicin P(DLLA-co-CL) cylinders into 0–80 g L^{-1} KCl eluent, 30% loading.

cylindrical shape was not retained during the release due to polymer relaxation in water at 37°C (e.g. a 34 ± 16·3% decrease in length was observed for 30–50% drug-loaded cylinders after 572 h in eluents, with 55% ϵ-caprolactone content in the polymer). The swelling and polymer wet weight change were not as significant as in the last two cases.

Release of gentamicin, benzylpenicillin, and cephazolin from drug/polymer/acetone suspension-extruded/coated cylinders

The coated-cylinder device was designed to improve the release properties. The cumulative release profiles for 20–50% loaded, 0·5–2 cm-long devices are shown in Fig. 5. For

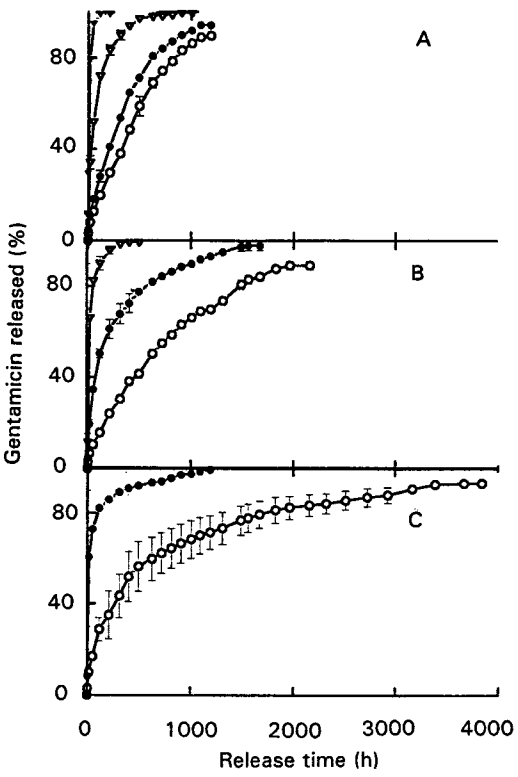

FIG. 5. Release of gentamicin sulphate from the coated PDLLA cylinders into distilled water. A. 0·5-cm long, loading (%) ○ 20, ● 30, ▽ 40, ▼ 50. B. 1-cm long, loading (%) ○ 30, ● 40, ▽ 50. C. 2-cm long, loading (%) ○ 40, ● 50.

high-loaded (40 and 50%) devices, release was dominated by the channel diffusion mechanism (Fig. 5). The release of 50%-loaded devices was faster than 40%-loaded devices. On the other hand, release from 20- and 30%-loaded devices was much more gradual and sustained than that from the 40- and 50%-loaded devices. This cannot be described by pure channel diffusion release. Since more drug can be carried by the 30%-loaded cylinder, it was chosen for further testing.

Since gentamicin cannot permeate through the coated cylinder wall, device length has a significant effect on the release profile. This gives a convenient way of adjusting the release rate and duration to meet specific requirements. The effect of device length was clearly shown for 0·2–1 cm-long 30%-loaded devices by measuring the release into distilled water and 20 g L^{-1} KCl (Figs 6,7). For example, the time required for 90% of the entrapped gentamicin to be released into water from cylinders with lengths of 0·2, 0·4 and 1 cm were 1000, 1700, and 2800 h, respectively.

In practice, a simple empirical equation to describe the release is desirable. For the coated cylinder with a 30% loading, the device with the most promising properties, the Monod (Bailey & Ollis 1986) equation can be used:

$$F = \frac{a \cdot t}{b + t} \quad (1)$$

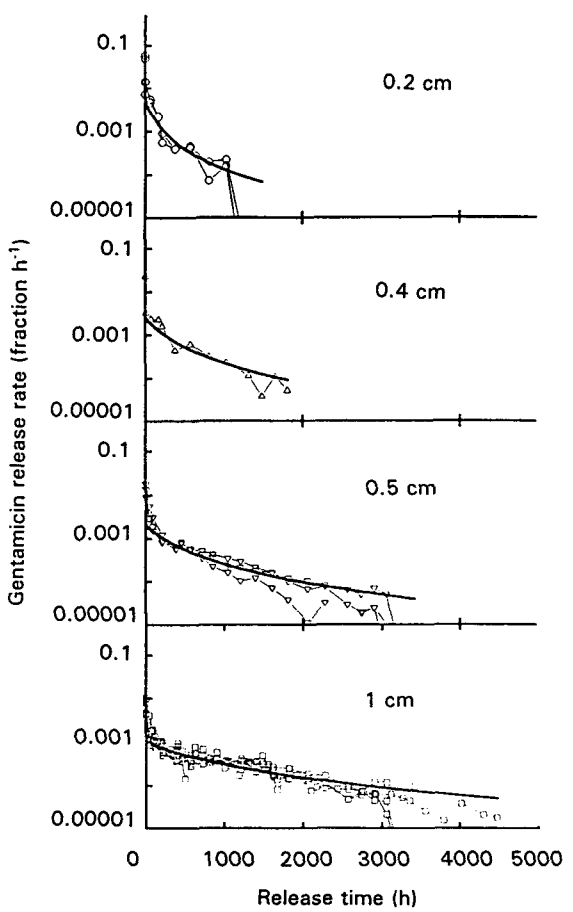

FIG. 6. Empirically interpreted (eqn 2) gentamicin release rates from the 0·2–1-cm long coated cylinders into water.

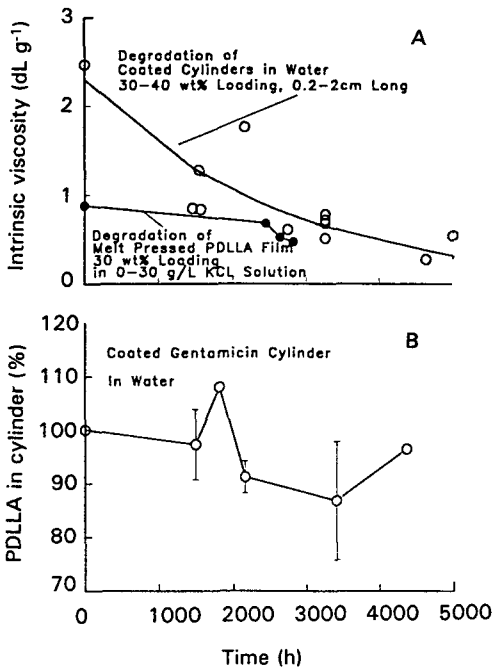

FIG. 7. A. Polymer mol. wt degradation of coated cylindrical and melt-pressed PDLLA film devices in water. B. Polymer mass loss of coated cylindrical devices in water.

where F is the released fraction, is release time, and a and b are constants, their values depending on the device length (L) and eluent salt concentration. For release into water $a = 0{\cdot}9134 + 0{\cdot}3678 \times L$, $b = -119{\cdot}8 + 907{\cdot}1 \times L + 384{\cdot}7 \times L^2$; for release into 20 g L^{-1} KCl, $a = 1{\cdot}036 - 0{\cdot}3935 \times L$, $b = -135{\cdot}9 + 1135{\cdot}2 \times L - 411{\cdot}6 \times L^2$. The release rate, then, will be:

$$\frac{dF}{dt} = \frac{a \cdot b}{(b + t)^2} \quad (2)$$

Equation 2 describes the majority of release data satisfactorily (Fig. 6, solid lines). Similar results were obtained for release into 20 g L^{-1} KCl.

Polymer mol. wt degradation of the cylinders in water after release was measured by the change in intrinsic viscosity in chloroform at 25°C (Fig. 7A). The degradation followed first-order kinetics (Pitt et al 1981) with a rate constant $k = 9{\cdot}3 \times 10^{-3}$ day^{-1}, which is faster than for a pure PDLLA film. The polymer mass loss of the device in water was not significant even over a period of 4500 h (Fig. 7B).

Benzylpenicillin is unstable in water due to hydrolysis of its β-lactam bond, especially in the presence of salt (Bird et al 1986). Although benzylpenicillin release could not be

Table 1. Release of benzylpenicillin from 30% loaded 1 cm-long cylinders into water.

	Released benzylpenicillin (%)			
Coating\release time (h)	5	10	15	25
None	15	18	20	22
Wall	6	8	10	10
Wall + one end	0	5	6	6
Total	0	0	0	0

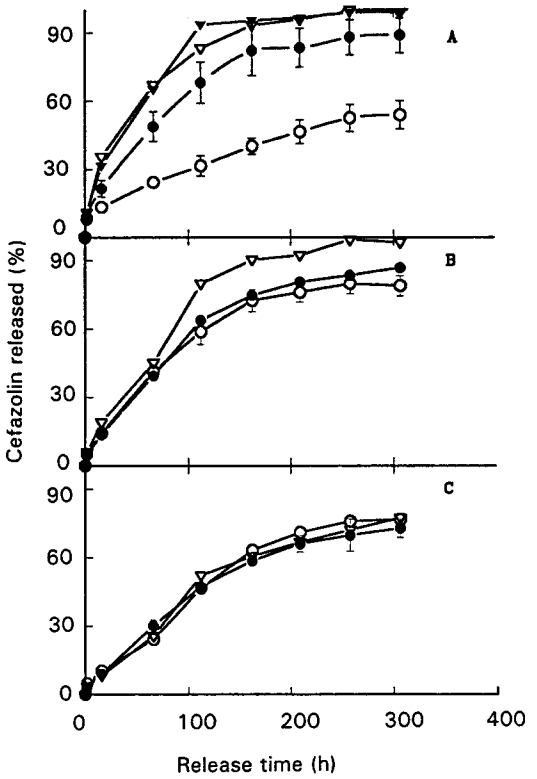

FIG. 8. Release of cephazolin sodium from PDLLA-coated cylinders in distilled water. A. 1-cm long, loading (%) ○ 20, ● 30, ▽ 40, ▼ 50. B. 2-cm long, loading (%) ○ 30, ● 40, ▽ 50. C. 4-cm long, loading (%) ○ 30, ● 40, ▽ 50.

detected after 76 h, the initial release showed a significant sustaining effect of the coating (Table 1).

Cephazolin is more stable than benzylpenicillin in water. The hydrolytic degradation of cephazolin follows first-order kinetics. The degradation rate constant k was found to be 0·038 day^{-1} in distilled water at 37°C, which is consistent with the literature value of 0·048 day^{-1} at 35°C (Yamana & Tsuji 1976). The cephazolin sodium release from the coated cylindrical devices is shown in Fig. 8. For 1 cm-long devices with 20–50% loading, release can be interpreted as channel diffusion, while release could have involved osmotic pressure effects for the longer devices (2 and 4 cm) and were similar for different drug loadings (30, 40, and 50%). The duration of release lasted no more than 300 h (Fig. 8).

The particle sizes of cephazolin and gentamicin were 485 ± 170 and $14{\cdot}9 \pm 8{\cdot}1\,\mu m$, respectively. The faster release of cephazolin from the coated cylinder compared with the release of gentamicin sulphate might be due to the fact that cephazolin had a much larger particle size than gentamicin, since a large particle size results in larger channels which in turn give a fast channel diffusion release.

Conclusions

Biodegradable controlled antibiotic release films and cylinders have been manufactured and their in-vitro release properties have been tested. The coated gentamicin sulphate PDLLA cylinders with 20 and 30% drug loading gave small initial bursts, and gradual and sustained release. Furthermore, the release rate and duration from these cylinders could be adjusted by cutting the cylinders into different lengths. The release from these coated PDLLA cylinders could be interpreted by a simple Monod equation as a function of cylinder length. Antibiotic release from the coated gentamicin/PDLLA cylinders with 40 and 50% loading was too fast for practical purposes. Cephazolin and benzylpenicillin were found to be unsuitable for a sustained release longer than 300 h due to their instability in water. On the other hand, gentamicin sulphate films and melt-extruded cylinders failed to give the desirable release properties of small initial burst, gradual, sustained, and complete release. Poly(D,L-lactide-co-ε-caprolactone), low mol. wt poly(D,L-lactic acid), and a mixture of D,L-lactic acid oligomer and high mol. wt poly(D,L-lactide) may not be good materials for making controlled antibiotic release devices due to their high flexibility in water and rapid mass loss, although these materials require processing temperatures of less than 110°C. The coated gentamicin/PDLLA cylinder with a 30% drug loading appears to be a promising antibiotic delivery device for treatment of bone infection in orthopaedic surgery.

Acknowledgements

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