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Drug release from PLA/PEG microparticulates

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Abstract

Drug-loaded biodegradable PLA, PLA/PEG microspheres were prepared by the coacervation technique, by solvent evaporation and by the emulsion method. The effects of drug properties, particle size, drug loading and method of microencapsulation on the in vitro drug dissolution were also examined. According to the results, PLA/PEG copolymer was more hydrophilic than PLA homopolymer, and with lower glass transition temperature. PLA/PEG microparticulates were not as smooth as that of PLA. Drug release from microspheres was effected by the properties of PLA/PEG copolymers. The release rate of the hydrophobic drug, lidocaine, encapsulated in the polymer PLA/PEG copolymer, was faster than that in a pure PLA homopolymer. The same results also held for the hydrophilic drug, propranolol hydrochloride. Microspheres obtained by the emulsion method were porous and with adequate drug permeability. © 1997 Elsevier Science B.V.

Keywords: Biodegradable polymers; PLA/PEG; Drug release; Microencapsulation

1. Introduction

The biodegradable polylactide (PLA) homo- and copolymers have been extensively investigated as drug carriers as they have been shown not to cause adverse tissue reaction (Leung et al., 1987; Lewis, 1990). Biodegradable polymeric carriers can be hydrolyzed in the body to form products that are easily resorbed or eliminated. Surgically removing these carriers or implants is unnecessary at the end of therapy or when the drug is depleted. Sampath et al. (1992) intended to fabricate poly(L-lactic acid) implants containing gentamicin sulfate for the treatment of osteomyelitis by prolonged localized delivery of drug. In their in vitro release test, cylindrical poly(L-lactic acid) implants obtained by compression of microcapsules, ranging from 278–444 μm, released an amount exceeding 80% gentamicin sulfate within 3 weeks. Meanwhile, Miyamoto et al. (1992) pointed that poly(DL-lactic acid) homopolymers with high molecular weights of 105 000, 21 000 and 3300

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were inappropriate as a bone morphogenetic protein (BMP) carrier, primarily because they produced strong foreign-body reactions or chronic inflammation and were too slowly absorbed to be replaced by induced bone. In addition, poly(L-lactic acid) degrades in the body to lactic acid. It creates a local acidic environment. The pH of a suspension of PLA (MW 650) in saline at a concentration of 1% wt/wt was 2.8 (Miyamoto et al., 1993). This event may exert an adverse effect on bone induction by BMP or bone formation, and must be considered in other applications whenever PLA homopolymers were applied.

Introducing polyethylene glycol (PEG) into polylactic acid homopolymers could increase the degradation rate, decrease the acidity of degraded products, and increase the hydrophilicity of the polymer carriers. Hydrophilic PEG segments in the PLA copolymers may also enhance the diffusivity of water or drug in the polymer carriers (Zhu et al., 1990).

In this study, the effects of PEG 'soft' segments added to the PLA co-polymer on the degradation, size distribution, drug content in microparticulates and release rate are investigated. The morphology and release behavior of microparticulates are also assessed. Two model drugs, lidocaine, a hydrophobic drug, and propranolol hydrochloride, a hydrophilic drug, are employed as well to investigate the interaction between the PLA/PEG and drugs.

2. Materials and methods

2.1. Materials

Lidocaine base and propranolol hydrochloride (Nacalai Tesque, Kyoto, Japan) were used as received. PEG (molecular weight 2000 or 6000) and PVA (degree of polymerization: 2000; viscosity of a 4% aqueous solution at 20°C: 35–45 cps) were also obtained from Nacalai Tesque.

Methylene chloride, chloroform and hexane, all L.C. grade, were obtained from Alps Chem Co. (Hsingchu, Taiwan). Commercial samples of PDLLA (molecular weight: 10 000), PLLA (molecular weight: 10,000) and lactide were purchased from DuPont (Wilmington, DE, USA). All other regents were of reagent HPLC grades, and used as received.

2.2. Fabrication of PLLA/PEG

PLA/PEG copolymer was synthesized from lactide dimer and PEG 2000, under an atmosphere of nitrogen, at 180°C. The reaction time is around 6 h (Hu and Liu, 1993).

2.3. Characterization

The methods of characterizing polymer synthesized were the same with Hu and Liu (1993). Briefly, ^{1}H-NMR spectrum was measured at 200 MHz with a Bruker AC200 spectrometer using tetramethylsilane (TMS) as the internal standard. Differential scanning calorimetry (DSC) was performed under a nitrogen atmosphere on a DuPont 912-2000 thermal analyser. The heating rate was set at 10°C/min with the sample amount of 10.0 mg. Gel permeation chromatography (GPC) was measured on a Waters 510 equipped with Waters 410 differential refractometer. Two Zorbax PSM Bimodal (6.2 mm I.D., length 25 cm) columns were used. Drug partition coefficients were measured from the amount of drug distributed in octanol/water to serve as a measure of the hydrophobic affinity of drug in the polymers.

2.4. Methods of microencapsulation

Solvent evaporation, coacervation (phase inversion) and emulsion methods were individually applied to encapsulate the model drug.

2.4.1. Solvent evaporation

Hydrophobic drug was easily encapsulated in PLA polymers by solvent evaporation. A solution of drug and copolymer (100 mg) in methylene chloride or chloroform (4 ml) was mixed well,then poured into a glass petri dish and dried under vacuum. A thin film or macro-flakes were formed after the organic solvent had evaporated. Then the thin film or macro-flake was milled and sieved (size fraction of 74–149 μm).

Table 1
The molecular weight and T_g of the resulting copolymers with PEG:PLA ratios 0, 3 and 9 wt% in feed

PEG wt% in feed	PEG wt% in copolymers (NMR)	Yield (%)	T_g (°C)	Molecular weight (M_n) (GPC)
0	—	—	58.9	78 964
3	5.4	86	44.8	19 812
9	15.8	85	42.7	10 133

2.4.2. Coacervation (phase inversion)

Drug encapsulated into polymers by coacervation was performed as described in Sampath et al. (1992). Briefly, a weighed quantity of PLA/PEG, normally, 1–2 g, was dissolved in methylene chloride to yield a 2.5% w/v solution. By using a magnetic stirrer which provided an agitation rate of approximate 500 rpm, a known quantity of model drug based on the drug loading, was suspended in the solution. To induce coacervation, an excess of hexane, normally 200–250 ml, which is a nonsolvent for PLA, was added at 2.5 ml/min with continuous stirring. The coacervation droplets adhered to the suspended drug particles and coalesced around them to form polymer microparticulates. The microparticulates were allowed to harden for 2 h, then decanted and washed twice with 50 ml of hexane. After final separation by decantation, the microparticulates were dried for 10–14 h at 35°C.

2.4.3. Emulsion and solvent evaporation

Encapsulating hydrophobic drug, a o/w emulsion technique was applied. A solution of drug and copolymer (100 mg) in methylene chloride or chloroform (4 ml) was rapidly poured into 20 ml of water containing 0.4 wt% of poly(vinyl alcohol). The mixture was sonicated for 15 minutes to form an emulsion, then changed to mechanically stirred. Stirring was continued until the organic solvent had evaporated. The microspheres were then separated, and dried under vacuum.

Encapsulating hydrophilic drug, a w/o/w emulsion technique was applied. Aqueous drug solution (1 ml) was first poured into the polymer solution (100 mg of polymer dissolved in 4 ml methylene chloride or chloroform) to form a w/o emulsion. The w/o emulsion was then rapidly poured into 20 ml of water containing 0.4 wt% of poly(vinyl alcohol) and then through the same process as described above.

2.5. Particle size and drug content

The particle size of the microparticulates was determined by photon correlation spectroscope (He/Ne laser particle size analyzer; Malvern Instrument, UK). Each batch sample of microparticulates was dissolved in methylene chloride and the drug content was determined using an UV spectrophotometer (Beckman DU-64, Palo Alto, CA), at a wavelength of 214 nm.

2.6. Dissolution test (release test)

Microparticulates, 0.1 g, were poured into a 7-mm diameter die and compressed under a hydrostatic pressure of 100 kg/cm^2. A tablet, 7 mm in diameter and 3 mm in thick, was formed.

The release (dissolution) tests were performed at 37°C in 0.025 M phosphate buffer pH 7.4 brought to ionic strength 0.13 with sodium chloride under static conditions (one tablet in 5 ml buffer). Data are the average of three replicates.

2.7. Assay

Drug concentration in the solution was assayed by capillary electrophoresis, with borate buffer, (pH 9.4,) as a running buffer. The sample mixture was separated by high voltage, 15 kV, and measured by UV detector at 214 nm.

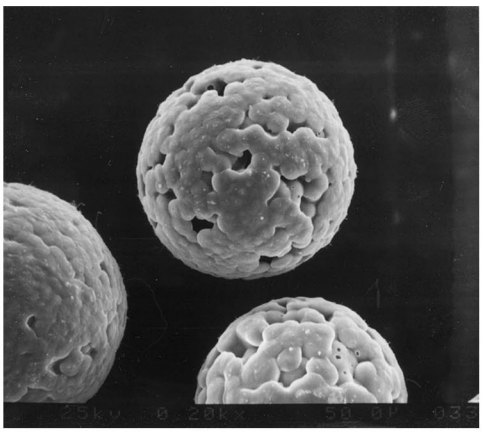
2.8. Morphology study

The morphological difference of microparticulates made of various PEG contents and resulting from different methods of encapsulation were

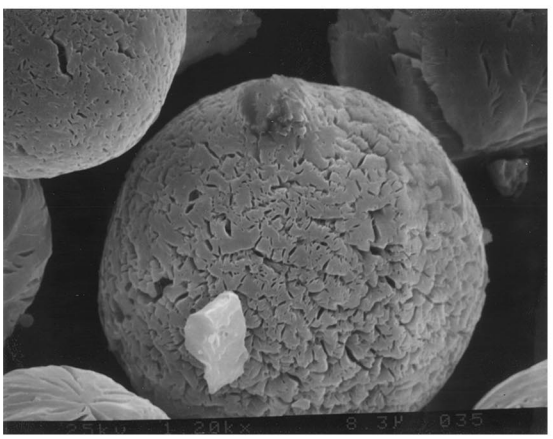
monitored by scanning electron microscopy (Olympus JSM-35, Tokyo, Japan).

3. Results and discussion

ABA block copolymers of polyethylene glycol and poly-L-lactic acid were prepared as previously described (Hu and Liu, 1993) by ring opening polymerization of L-lactide with polyethylene glycol, M_n 2000. The effect of PEG content on the molecular weight of PEG/PLA copolymer is shown in Table 1. The molecular weight of PEG/PLA copolymer decreases with increasing content of PEG.



(A). Made from PLA Homopolymer



(B). Made from PLA/PEG Copolymer

Fig. 1. Particle morphology. (A) Microspheres made from PLA homopolymer, × 2000. (B) Microspheres made from PLA/PEG copolymers, × 2000.

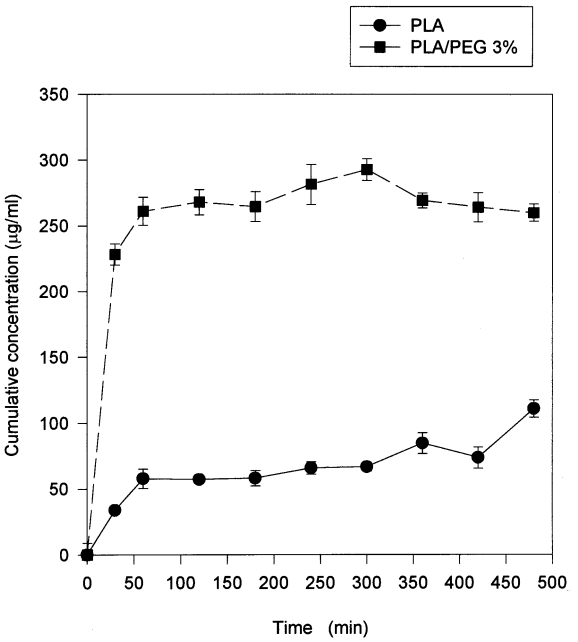


Fig. 2. Drug release from a PLA homopolymer and PLA/PEG copolymers.

The ratio of PEG in the resulting copolymers, PEG/PLA, was higher than the ratio in feed. This was probably due to the hydrophilicity of PEG in the reaction mixture that causes a reduction of reactivity of the lactide. Consequently, the copolymer molecular weights were lower than those of the homopolymers. As the PEG wt% increased, the molecular weight and T_g decreased.

PLA thin films were formed when the solvent evaporation method was employed to encapsulate the drugs, while micro-flakes were formed when 3 wt% PEG/PLA copolymers were used instead of PLA homopolymers. Microparticulates were formed when the coacervation technique was used. The resulting powder of microparticulates of PLA were smoother than the powder made from the PEG/PLA copolymers. Spherical particles were obtained when the emulsion method was employed. The particle size of the PLA homopolymer was smaller than that made from the PLA/PEG copolymer under the same conditions. The particle size and morphologies of the micro-

spheres made by different materials are shown in Fig. 1. Significantly, different pore structures are found. Microspheres of PLA have large pores but with integrity in sub-surface regions, while microspheres made from PLA/PEG have straight open channels.

Fig. 2 reveals lidocaine release profiles from PLA homopolymer and PLA/PEG copolymer. PLA is hydrophobic while PEG/PLA is more hydrophilic. As a result, drug release is faster from PEG/PLA copolymer than that from PLA homopolymer because of the higher hydration rate and swelling characteristics of the ethylene glycol. Water easily interacts with the hydrophilic segments in the PEG/PLA copolymers and hydrates the spheres. The polymer of PEG/PLA takes up more water than the PLA homopolymer, as a result, the copolymer swells and becomes more porous. In the partition-dependent diffusional transport polyester copolymer, a larger porous membrane increases the diffusion rate of the penetrant.

Despite the hydrophobicity of PLA, crystallinity and water uptake are prominent factors in delivery and in determining the rates of in vitro and in vivo degradation. From the DSC thermograph, the crystallinity in PLA is higher than that in PLA/PEG. The more hydrophilic the copolymer, the lower its crystallinity. Low crystallinity in the polymer matrix means lower diffusional barriers.

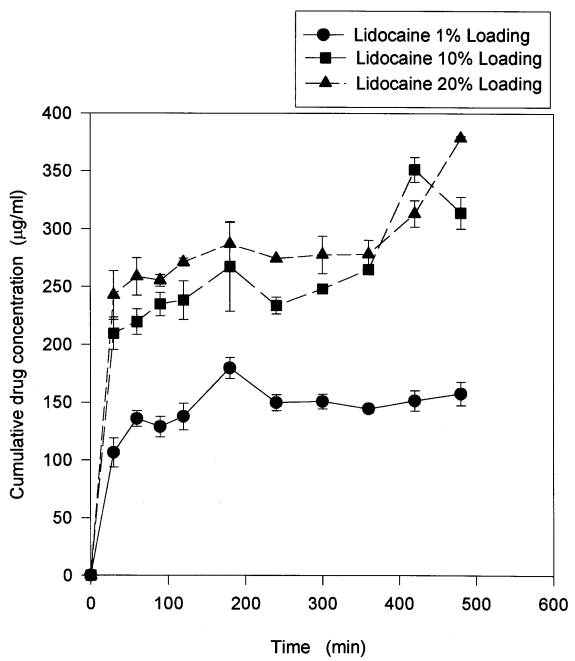


Fig. 3. Drug-loading versus release rate of microparticulates.

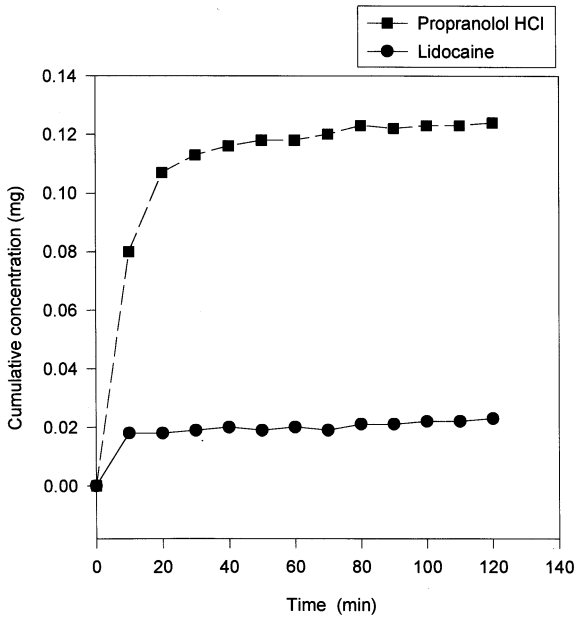


Fig. 4. Comparison of the release rate of lidocaine (base) and propranolol hydrochloride from microparticulates made from PLA/PEG 3%wt (refer to Table 1).

Drug loading is also a significant factor influencing drug release. Fig. 3 reveals the different lidocaine loading on the cumulative release amount of microparticulates made by 3 wt% PEG/PLA copolymer using the phase inverse technique. High drug loading caused the drug to be released more quickly. Because the partition coefficient of lidocaine is around 81, it is assumed that drug was dissolved in the polymer matrix of polyester copolymer. Higher drug density would cause a low polymer density in the matrix, thereby would reducing the diffusional barrier.

Compared to the hydrophobic drug, lidocaine, the release rate of propranolol hydrochloride was more rapid, as shown in Fig. 4. Propranolol hydrochloride has a low solubility in the polymer. Because the partition coefficient of propranolol hydrochloride is about 0.081, this implies that

most of drug may crystallize on the polymer surface and accumulate, rather than dissolving in the copolymer matrix during the encapsulation process. For most biodegradable polyester polymers, diffusional transport is the dominating mechanism of release in the early stages. Hydrophilic drug was easily dissolved and release achieved through the porous channels. By pure diffusion through the porous channel, high drug loading yields faster release (Fig. 5).

Fig. 6 showed that drug in the PEG 9 wt% copolymer is released more quickly than that in 3 wt% PEG in the copolymer. Owing to the higher hydration of PEG in the PLA/PEG copolymer, microspheres made from these copolymers were less well formed. High interactions between the PLA/PEG and the nonsolvent (water in emulsion process) favored the formation of macrovoids (McKelvey and Koros, 1996). Release rate is associated with water uptake, which is biphasic, reflecting the contribution of two processes: rapid diffusion of water into the initially miscible PEG

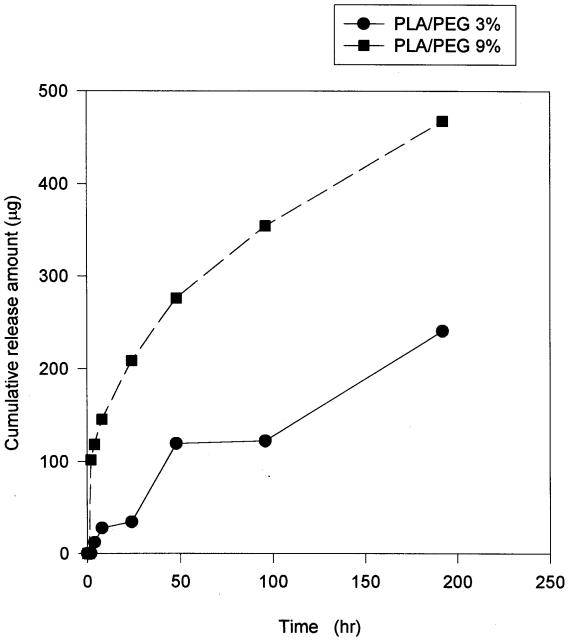


Fig. 6. Drug release from PLA/PEG 3 %wt and PLA/PEG 9 %wt microspheres.

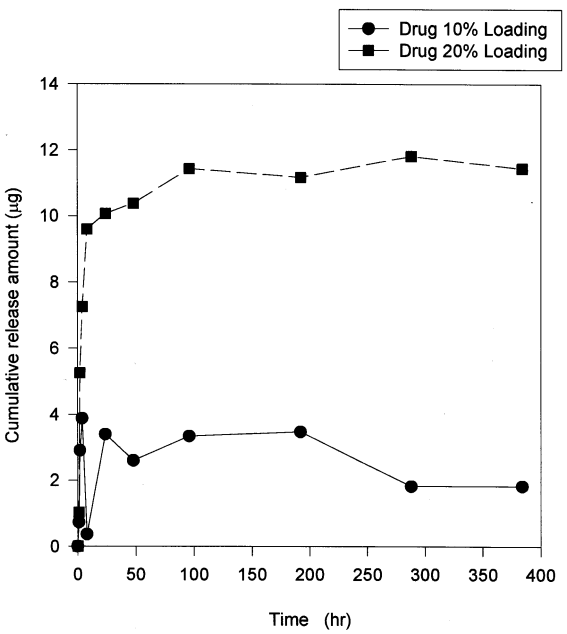


Fig. 5. Cumulative release from microparticulates made from 9 %wt PEG/PLA copolymer using the w/o/w emulsion solvent evaporation.

and PLA blocks; then a slower rate of hydration possibly due to phase separation and hydrolytic cleavage of the PLA block (Shah et al., 1995). A larger burst was also observed in the dissolution test.

Different encapsulating methods did not have a significant effect on drug release rate if the particle size is kept constant, in contrast to what we predicted—that different encapsulating method would influence the microparticulates structure and release mechanism. In the phase inversion, lowering initial polymer concentration moves the mass transfer paths closer to the critical point where spinodal-like structure formation would be expected. Increased polymer concentrations lead to reduced transport rates and tend to move the point of precipitation to the metastable region of the phase diagram where nucleation and growth mechanisms predominate. In the case of lower initial polymer concentrations, the interconnected network, in general, favors greater skin surface porosity resulting in higher membrane permeability (McHugh and Tsay, 1992).

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References

Hu, D.S., Liu, H.J., 1993. Effect of soft segment on degradation kinetics in polyethylene glycol/poly(L-lactide) block copolymers. Poly. Bull. 30, 669–676.

Leung, S.S., Lee, V.H.L., Robinson, J.R., 1987. Parenteral products. In: Robinson, J.R., Lee, V.H.L. (Eds.), Controlled Drug Delivery: Fundamentals and Applications, Dekker, New York, pp. 433–480

Lewis, D.H., 1990. Controlled release of bioactive agents from lactide/glycolide polymers. In: Chasin, M., Langer, R. (Eds.), Biodegradable Polymers as Drug Delivery Systems, Dekker, New York, pp. 1–41.

McHugh, A.J., Tsay, C.S., 1992. Dynamics of the phase inversion process. J. Appl. Polym. Sci. 46, 2011–2021.

McKelvey, S.A., Koros, W., 1996. Phase separation, vitrification, and the manifestation of macrovoids in polymeric asymmetric membranes. J. Membr. Sci. 112, 29–39.

Miyamoto, S., Takaoka, K., Okada, T., Yoshikawa, H., Hashimoto, J., Suzuki, S., Ono, K., 1992. Evaluation of polylactic acid homopolymers as carriers for bone morphogenetic protein. Clin. Orthop. 278, 274–282.

Miyamoto, S., Takaoka, K., Okada, T., Yoshikawa, H., Hashimoto, J., Suzuki, S., Ono, K., 1993. Polylactic acid-polyethylene glycerol block copolymer-A new biodegradable synthetic carrier for bone morphogenetic protein. Clin. Orthop. Related Res 294, 333–343.

Sampath, S.S., Garvin, K., Robinson, D.H., 1992. Preparation and characterization of biodegradable poly (L-lactic acid) gentamicin delivery systems. Int. J. Pharm. 78, 165–174.

Shah, S.S., Zhu, K.J., Pitt, C.G., 1995. Poly-DL-lactic acid: polyethylene glycol block copolymers. The influence of polyethylene glycol on the degradation of poly-DL-lactic acid. J. Biomater. Sci. Polym. Edn. 5, 421–431.

Zhu, K.J., Lin, X., Yang, S., 1990. Preparation, characterization, and properties of polylactide (PLA)-poly(ethylene glycol) (PEG) copolymers: a potential drug carrier. J. Appl. Polym. Sci. 39, 1–9.

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