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The effect of the addition of low molecular weight poly(DL-lactide) on drug release from biodegradable poly(DL-lactide) drug delivery systems

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Summary

Biodegradable films and microspheres were prepared from blends of high and low molecular weight poly(DL-lactide) with molecular weights of 120,000 and 2000, respectively, by solvent casting and an emulsification–solvent evaporation method. Salicylic acid, caffeine, and quinidine were chosen as model compounds. Differential scanning calorimetry and scanning electron microscopy were used to characterize the films and microspheres. The addition of low molecular weight poly(DL-lactide) clearly accelerated the release of drug from both films and microspheres. Biodegradable drug delivery systems were prepared with durations of action between several hours to months by varying the amount of low molecular weight poly(DL-lactide). This technique allowed control over the drug release with a single, biodegradable homopolymer. In the case of quinidine, interactions with the carboxyl groups of poly(DL-lactide) occurred and complicated the release pattern.

Introduction

In the majority of novel drug delivery systems, control of drug release is effected by using various properties of polymeric drug carriers. The permeability of a polymer for a particular drug molecule depends among other factors, on the polymer composition. The polymer composition can be varied with respect to copolymer ratio, sequential distribution of the copolymers, molecular weight and molecular weight distribution, and crystallinity. Permeation rates through polymers can also be enhanced or reduced by suitable additives such as plasticizers of fillers. If these novel dosage forms are designed for parenteral administration, the use of biodegradable and biocompatible polymers and release-controlling adjuvants is required.

The biodegradability and biocompatibility of polyesters such as poly(glycolide) (PGA) and poly(lactide) (PLA) and their respective copolymers have been well established from their uses in surgical sutures, grafts, implants, and various prosthetic devices. Considerable interest has evolved in the use of these materials as drug carrier materials. Techniques such as film casting (Jackanizc et al., 1973), microencapsulation (Beck

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et al., 1979), molding (Schwope et al., 1975), and spray-drying (Deligiannis et al., 1987) have been applied to the preparation of biodegradable dosage forms for the delivery of drugs such as anticancer drugs, fertility-control agents, and narcotic antagonists.

Drug release from biodegradable polyesters is often too slow, especially at low drug loadings. The permeability of PLA membranes has been increased by incorporating pore-forming additives, such as glycerin, or plasticizers, such as tributyl citrate and phthalate esters to reduce the glass transition temperature of the polymer (Pitt et al., 1979). Juni et al. (1985) increased the drug release rate from PLA microspheres by adding fatty acid esters during the preparation of the microspheres.

The objectives of this investigation were to prepare biodegradable films and microspheres from blends of low and high molecular weight PLA and to show that drug release could be controlled by varying the amount of low molecular weight PLA. This technique would allow the control of drug release with only one polymer and it would obviate the necessity of using other, potentially toxic release-controlling adjuvants.

Materials and Methods

Materials

High molecular weight poly(DL-lactide) (high MW-PLA, mol. wt. = 120,000) (Southern Research Institute, Birmingham, AL) and a low molecular weight poly(DL-lactide) (low MW-PLA, mol. wt. = 2000) (Boehringer Ingelheim, F.R.G.) were used. The following chemicals were obtained from commercial suppliers and used as received: caffeine (MCB Manufacturing Chemist, Gibbstown, NJ), quinidine, salicylic acid (Sigma Chemical Co., St. Louis, MO), acetone and methylene chloride (Fisher Scientific Co., Fair Lawn, NJ).

Methods

Two monolithic delivery systems of different shape and surface area were evaluated. The films were prepared by casting a common solution of drug (caffeine, salicylic acid, or quinidine) and the PLA blend (350 mg) in methylene chloride or acetone (7 ml) into petri dishes (5.7 cm in diameter). The drug concentrations are expressed on a w/w basis in the text. The films were dried at room temperature in a laboratory hood for two weeks and left in the petri-dishes.

Microspheres were prepared by the solvent evaporation method described previously (Bodmeier and McGinity, 1987a). A solution of the polymer blend (350 mg) and quinidine (150 mg) in methylene chloride (10 g) was emulsified into an aqueous phase (1.4 kg pH 10 borate buffer). The microspheres were collected after solvent evaporation by filtration, washed, dried, and sieved into various size fractions.

The PLA blends were made in mass ratios of 100/0, 75/25, 50/50, 25/75 and 0/100 for films, and 100/0, 90/10, 80/20, 70/30, 60/40, 50/50 and 40/60 for microspheres. In all designations of mass ratios, the high MW-PLA is listed first.

The release properties of the microspheres were studied using a rotating bottle apparatus. The microspheres (20–30 mg, 45–75 μm) were suspended in test tubes containing 50 ml of pH 7.4 phosphate buffer at 37 °C and rotated at 26 rpm. The polymeric films (diameter = 5.7 cm, film thickness = 90–120 μm) adhered strongly to the surfaces of the petri dishes and they were left in the petri dishes for the dissolution studies. The film edges were sealed with vacuum grease in order to avoid the penetration of the dissolution medium under the film. The USP XXI rotating paddle apparatus was used at 50 rpm to examine drug release from the polymeric films into 500 ml pH 7.4 phosphate buffer at 37 °C. All samples were run in triplicate. Quinidine, caffeine, and salicylic acid were assayed spectrophotometrically at the respective wavelengths of 237, 273 and 297 nm.

A computer-interfaced differential scanning calorimeter (Perkin-Elmer DSC II) equipped with a low temperature environmental chamber was used to obtain the thermal transitions. The samples of films (3–5 mg) and microspheres (3–5 mg, 45–75 μm) were analyzed at a 20 K/min heating rate in a nitrogen atmosphere. The temperature calibration was done with the melting transition of indium.

Scanning electron microscopy (SEM) was used to characterize the film and microsphere structure before and after the dissolution study. The dried samples were coated for 70 s under an argon atmosphere with gold-palladium (Pelco Model 3 Sputter coater) and observed with a Jeol JSM 35C scanning electron microscope.

Results and Discussion

The model compounds for the preparation of solvent-cast films were water-soluble drugs, salicylic acid, caffeine, and quinidine, respectively. Transparent, crystal-free films were obtained at caffeine concentrations smaller than 2.8% and at salicylic acid concentrations smaller than 7.2%. The drugs crystallized outside the polymeric matrix at high concentrations. Figs. 1 and 2 show the release of caffeine and salicylic acid from films prepared from varying ratios of high and low MW-PLA. No cracks or imperfections were seen on the film surface prior to the dissolution study as indicated by scanning electron microscopy. The films remained intact during the course of the dissolution study with the exception of films prepared from pure low MW-PLA which disintegrated. Both drugs were released slowly from films prepared from pure high MW-PLA. The drug release was controlled by adjusting the amount of low MW-PLA added during film preparation. Increasing amounts of low MW-PLA clearly accelerated the release of both caffeine and salicylic acid. The faster drug release could be attributed to a reduction of the glass transition temperature, T_g, of the film, and to eventual leaching of the low MW-PLA during the dissolution study. DSC-thermograms of drug-free films showed a decrease in the T_g with increasing low MW-PLA content (Fig. 3). The polymer samples were completely miscible in all ratios, as indicated by a single T_g and by the formation of optically clear films. The T_gs of the blends were intermediate between the T_g of each polymer. The permeability of the polymer films for the drug

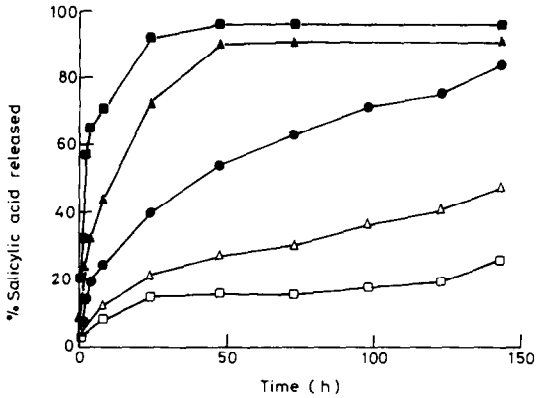


Fig. 2. Drug release from salicylic acid (6.7%)–poly(DL-lactide) films; high MW-PLA/low MW-PLA: (□) (100/0; (△) 75/25; (●) 50/50; (▲) 25/75; (■) 0/100.

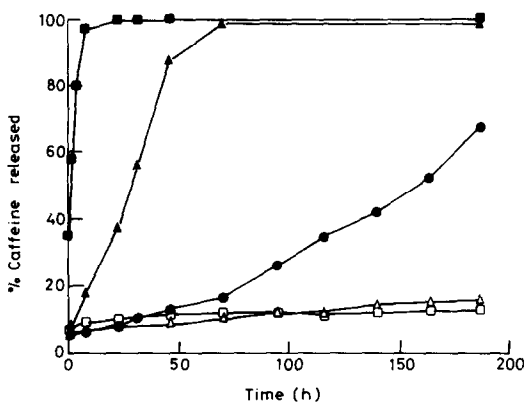


Fig. 1. Drug release from caffeine (2.8%)–poly(DL-lactide) films; high MW-PLA/low MW-PLA: (□) 100/0; (△) 75/25; (●) 50/50; (▲) 25/75; (■) 0/100.

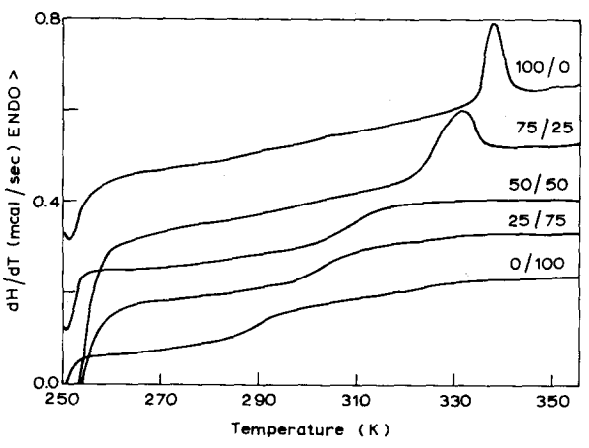


Fig. 3. DSC thermograms of poly(DL-lactide) films prepared from blends of high and low molecular weight poly(DL-lactide).

molecules increased with a decrease in T_g because the number of endgroups, and hence the free volume, increased with increasing amounts of low MW-PLA. An endothermic overlap at the T_g (Wunderlich, 1981) was observed with films prepared from blends with a ratio of 100/0 and 75/25. This endothermic peak represented the energy necessary to overcome the microstructure of the polymer film which developed during solvent casting. The peaks disappeared after melt-quenching the samples. The endothermic peak was absent in films containing more than 50% low MW-PLA. The solubility of a polymer in a particular solvent generally decreases with increasing molecular weight. Films prepared from high molecular weight polymeric fractions therefore precipitated earlier during solvent evaporation resulting in more porous and structured films than films cast from low MW-PLA which did not have this peak. The free volume within the polymer dense region can still be very low.

The release of quinidine from films was more complex and was dependent on drug loading (Fig. 4A–C). Films prepared from high MW-PLA only resulted in the slowest, almost negligible drug release at all loading levels. The addition of low MW-PLA generally increased drug release, but no clear pattern was observable. The drug release from pure low MW-PLA films was slower than expected. Three competing factors, i.e. the solubility of the drug in the polymer film, the T_g of the polymer blend, and drug–polymer interactions, have to be considered to explain the release of quinidine from PLA blends. The films increased in transparency and became clear with increasing amounts of low MW-PLA at the same quinidine level. High MW-PLA films had a milky, but uniform appearance. This indicated an increased solubility of quinidine in the films with increasing low MW-PLA content. Quinidine did not interfere with the formation of homogeneous films; the crystals were dispersed uniformly within the polymeric matrix when compared with salicylic acid or caffeine which crystallized to a large extent outside the polymeric matrix. The drug release mechanism will differ depending on whether the drug solubility in the polymer film is exceeded or not (Langer, 1980). Leaching through aqueous pores

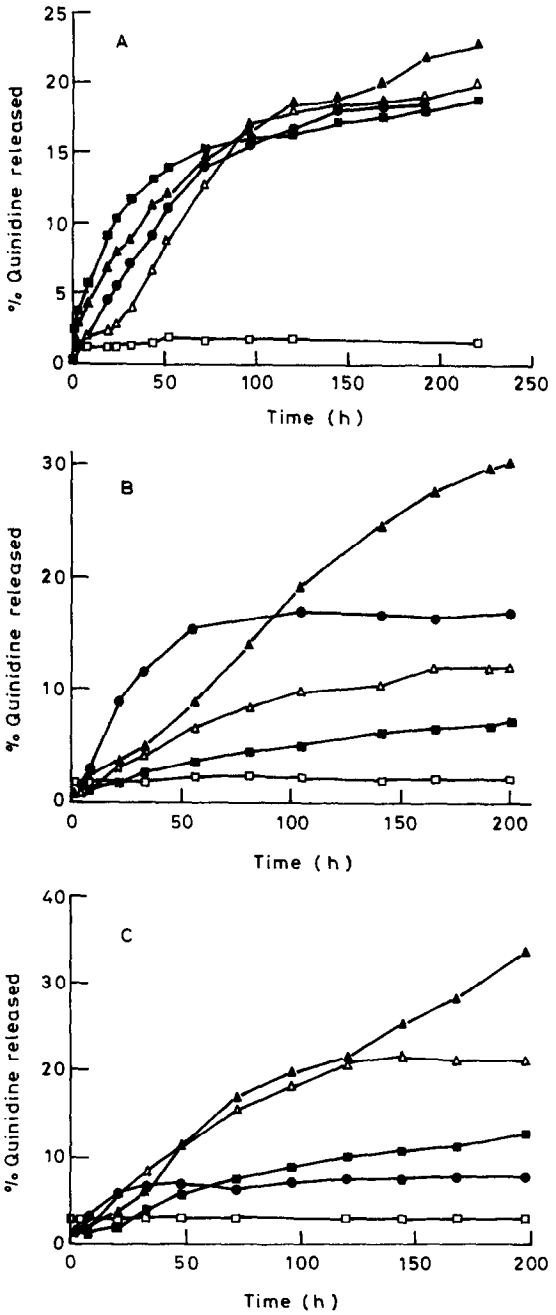
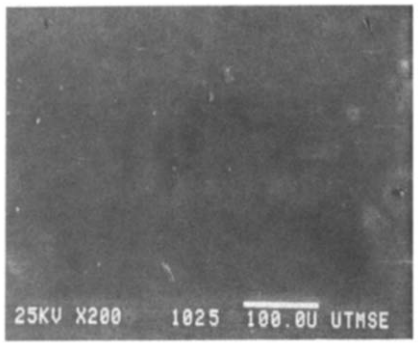


Fig. 4. Drug release from poly(DL-lactide) films containing different amounts of quinidine: (A) 12.5% quinidine; (B) 17.6% quinidine; (C) 22.5% quinidine; high MW-PLA/low MW-PLA: (□) 100/0; (△) 75/25; (●) 50/50; (▲) 25/75; (■) 0/100.



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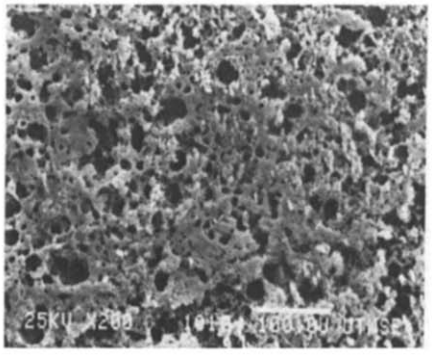

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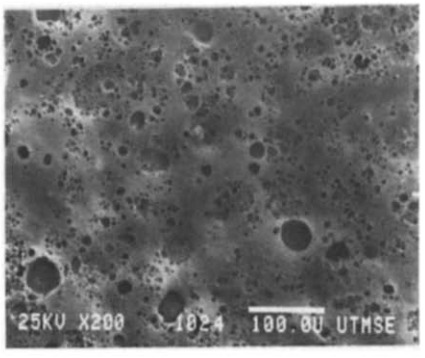

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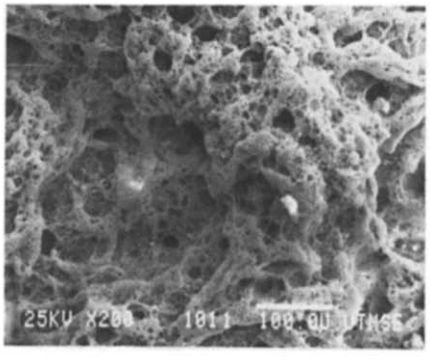

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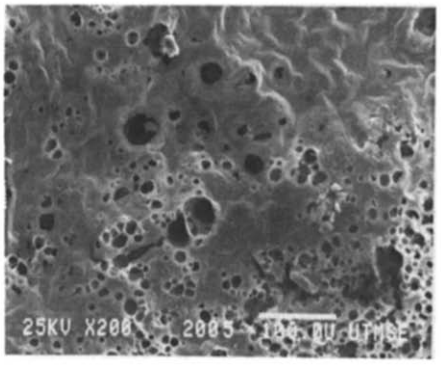

E

Fig. 5. Scanning electron micrographs of quinidine–poly(DL-lactide) films after dissolution studies; high MW-PLA/low MW-PLA-quinidine content (%): (A) 50/50 – 12.5%; (B) 25/75 – 12.5%; (C) 25/75 – 17.6%; (D) 0/100 – 12.5%; (E) 0/100 – 17.6%.

may contribute to the drug release in addition to drug diffusion through the polymer in films prepared from blends with larger amounts of high MW-PLA, in which the drug solubility was exceeded. On the other hand, the T_g and hydrophobicity of the polymer films decreased with increasing low MW-PLA content. The water penetration into the films may have increased because of the increased number of ionizable carboxyl groups. It was assumed that the carboxyl groups were in the ionized form at the pH of the dissolution medium (pH 7.4). This would contribute to an increase in drug release with increasing low MW-PLA fractions.

The interactions of several amine drugs including quinidine sulfate with polycarboxyl acid ion-exchange resins have been described by Borodkin et al. (1970). We believe that similar interactions occurred in this study and that these interactions became more dominant in films with high/low MW-PLA content. The end groups of PLA are carboxyl groups which could interact with basic compounds such as quinidine at the pH of the dissolution medium. Increasing the amount of low MW-PLA in the polymer blend will increase the number of free carboxyl groups and therefore the potential interactions with quinidine. This interaction could result in the formation of an insoluble drug–carrier complex or salt. SEM micrographs taken of the quinidine films after completion of the dissolution study are shown in Fig. 5A–E. All films had a smooth surface before the dissolution study. Films prepared from blends with ratios of 100/0, 75/25 and 50/50 had a smooth surface after the dissolution study. Irregular surfaces were observed with films prepared from blends with ratios smaller than 50/50. Films of low MW-PLA containing caffeine or salicylic acid disintegrated completely while films containing quinidine did not. The surface of films prepared from ratios of 25/75 and 0/100 became less irregular with increasing quinidine content which could indicate the formation of an insoluble polymer–drug layer and explain the reduction in drug release. The drug–carrier interaction could explain the irregular dissolution behaviour of quinidine containing films.

The preparation and evaluation of PLA microspheres was reported previously (Bodmeier and McGinity, 1987a and b). Microspheres were prepared similarly in this study by the solvent evaporation method, but the polymer fraction was composed of blends of low MW-PLA and high MW-PLA. The solvent evaporation method is limited to the entrapment of water-insoluble drugs when using an aqueous phase as the external phase. The model drug selected was quinidine, a base, which is poorly soluble at alkaline pH values. It can be entrapped within the microspheres by adjusting the pH of the aqueous phase to pH values of low drug solubility. The resulting microspheres were spherical and had a smooth surface. The formation of microspheres was not possible at ratios smaller than 25/75. The release of quinidine was more rapid from microspheres because of the larger surface area when compared with the films. In addition, the microstructure of the microspheres differed from that of the films. The microspheres have a sponge-like structure with the drug being primarily located within pores. Drug release from microspheres occurred mainly by leaching through pores (Bodmeier and McGinity, 1987b). Drug release from the films was controlled primarily by diffusion and to a lesser extent by leaching, especially in cases where the drug was completely soluble in the polymer film. Three different release phases were distinguishable for PLA microspheres as shown in Fig. 6. A lag time with no drug release was followed by a so-called burst

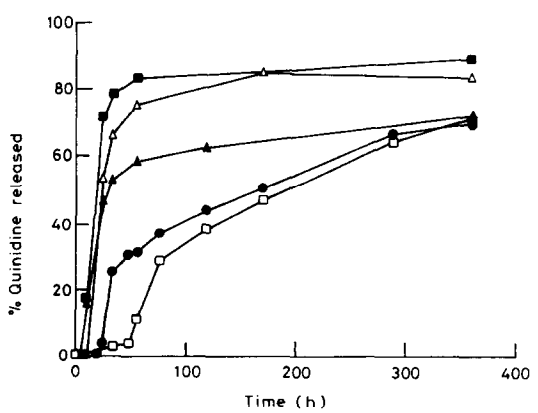

Fig. 6. Drug release from quinidine (23%)–poly(DL-lactide) microspheres; high MW-PLA/low MW-PLA: (□) 100/0; (●) 90/10; (△) 80/20; (■) 60/40; (▲) 40/60.

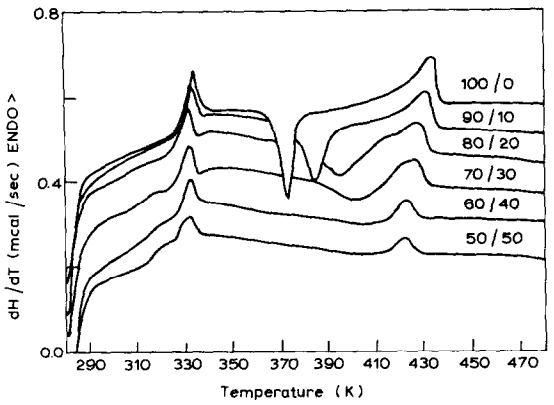

Fig. 7. DSC thermograms of quinidine (23%)–poly(DL-lactide) microspheres prepared from blends of high and low molecular weight poly(DL-lactide).

effect of rapid drug release within a short period of time, followed again by a slow release phase. The addition of low MW-PLA clearly accelerated the drug release. The lag time was shortened and the total amount released increased. Water penetration into the microspheres with subsequent rapid release of the drug through the pores (burst effect) occurred more rapidly with increasing low MW-PLA fractions due to the decrease in T_g.

A DSC-thermogram of the microspheres is shown in Fig. 7. Three thermal events were detectable, corresponding to the T_g of the polymer, and to the recrystallization and melting of quinidine. As already observed with the films, an endothermic peak overlayed the T_g. The ordered microstructure which developed during the microsphere preparation within the polymer matrix had to be overcome during the heating process. Only minor shifts in the T_g of microspheres were seen when compared with the pronounced changes in the T_g of films. However, a second-order transition preceding the endothermic overlap became more visible with increasing amounts of low MW-PLA. The solvent evaporation method is limited to the entrapment of compounds insoluble in the external phase. Water-soluble low molecular weight polymeric fractions could be lost to the aqueous phase during the formation of the microspheres thus resulting in a less than expected reduction in the T_g. The exothermic peak in the thermogram defined the temperature at which recrystallization of the amorphous phase of quinidine occurred. The size of the recrystallization peak of quinidine decreased and the peak shifted to higher temperatures with increasing low MW-PLA content. It disappeared at ratio smaller than 60/40. Quinidine dissolved in the PLA solution and it could precipitate within the microspheres during polymer precipitation in either a crystalline or amorphous form or it could be present in a molecularly dispersed state within the PLA matrix. The increase in recrystallization temperature suggests a stabilizing effect of the low MW-PLA on the amorphous fractions. An opposite trend was initially expected since polymer chain mobility increases with decreasing molecular weight. This should allow nuclear growth and recrystallization of the amorphous fractions at lower temperatures in samples containing higher fractions of low MW-PLA. However, not only the conditions during the run of the DSC sample or the transformation of the amorphous into the crystalline drug, but also the formation of the amorphous fractions during microsphere formation could influence the recrystallization temperature. The viscosity of the casting solution decreased with an increasing amount of low MW-PLA. Different degrees of ordering of the drug molecules can occur during the microsphere formation. The drug will precipitate within the microsphere matrix. A lower polymer solution viscosity at the point of drug precipitation would enhance the formation of more stable forms. This would explain the increase in recrystallization temperature with increasing low MW-PLA fractions. The interaction between the carboxyl groups and quinidine could also cause the increase in the recrystallization temperature with increasing low MW-PLA content. However, these interactions should occur to a lesser extent in microspheres, where the drug is primarily located in the pores when compared to films, where the drug is in intimate contact with the polymer molecules. The peak area of the melting transition endotherm of quinidine was reduced and shifted to slightly lower temperatures with increasing amounts of low MW-PLA. The melting endotherm corresponds to the drug undissolved in the polymer at the melting temperature. The peak size depends on the solubility of the drug in the

polymer at the melting temperature. The solubility of the drug in a polymer increases with decreasing molecular weight thus explaining the decreased peak area. The detection limit of quinidine in the microspheres with differential scanning calorimetry depended on the molecular weight of the polymer and it increased with decreasing molecular weight.

In conclusion, biodegradable films and microspheres were successfully prepared from blends of high molecular weight poly(DL-lactide) (mol. wt. = 120,000) and low molecular weight poly(DL-lactide) (mol. wt. = 2000). The drug release depended on the amount of low MW-PLA used. Biodegradable drug delivery systems were prepared with different durations of action. This technique allows control over the drug release with a single, biodegradable homopolymer. It could circumvent the potential toxicity problems inherent in other drug release-modifying additives frequently employed in controlled drug delivery systems, especially if these systems are designed for parenteral use.

References

Beck, L.R., Cowsar, D.R., Lewis, D.H., Cosgrove, R.J., Riddle, C.T., Lowry, S.L. and Epperly, T., A new long-acting injectible microcapsule system for the administration of progesterone. *Fertility and Sterility*, 31 (1979) 545–551.

Bodmeier, R. and McGinity, J.W., Polylactic acid microspheres containing quinidine base and quinidine sulfate prepared by the solvent evaporation technique: I. Methods and morphology. *J. Microencaps.*, 4 (1987a) 279–288.

Bodmeier, R. and McGinity, J.W., The preparation and evaluation of drug-containing poly(DL-lactide) microspheres formed by the solvent evaporation method. *Pharm. Res.*, 4 (1987b) 465–471.

Borodkin, S. and Yunker, M.H., Interaction of amine drugs with a polycarboxylic acid ion-exchange resin. *J. Pharm. Sci.*, 59 (1970) 481–486.

Deligiannis, C., Pramar, Y. and Bodmeier, R., Preparation of biodegradable microparticulates using a spray-drying technique. *Abstracts of the 47th International Congress of Pharmaceutical Sciences of F.I.P.*, September (1987) 114.

Jackanicz, T.M., Nash, D.I., Wise, D.L. and Gregory, J.B., Polylactic acid as a biodegradable carrier for contraceptive steroids. *Contraception*, 8 (1973) 227–234.

Juni, K., Ogata, J., Matsui, N., Kubota, M. and Nakano, M., Control of release rate of bleomycin from polylactic acid microspheres by additives. *Chem. Pharm. Bull.*, 33 (1985) 1609–1614.

Langer, R., Polymeric delivery systems for controlled drug release. *Chem. Eng. Commun.*, 6 (1980) 1–48.

Pitt, C.G., Jeffcoat, A.R., Zweidinger, R.A. and Schindler, A., Sustained drug delivery systems. I. The permeability of poly(ε-caprolactone, poly(DL-lactic acid), and their copolymers. *J. Biomed. Mater. Res.*, 68 (1979) 497–507.

Schwope, A.D., Wise, D.L. and Howes, J.F., Lactic/glycolic acid polymers as narcotic antagonist delivery systems. *Life Sci.*, 17 (1975) 1877–1886.

Wunderlich, B., Determination of the history of a solid by thermal analysis. In Turi, E.A. (Ed.), *Thermal Analysis in Polymer Characterization*, Heyden, Philadelphia, 1981, pp. 1–23.