Effect of the Inclusion of PEG on the Solid-State Properties and Drug Release from Polylactic Acid Films and Microcapsules

Sriramakamal Jonnalagadda,[1] Dennis H. Robinson[2]

[1]*Department of Pharmaceutical Sciences, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, Philadelphia, Pennsylvania 19104*
[2]*Department of Pharmaceutical Sciences, University of Nebraska Medical Center, 986025 Nebraska Medical Center, Omaha, Nebraska 69198-6025*

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ABSTRACT: The use of poly(lactic acid) (PLA) for controlled drug delivery applications was limited by unfavorable physical properties such as hydrophobicity, high intrinsic crystallinity, low permeability, and high glass transition temperatures. This research used polyethylene glycols (PEGs) of varying molecular weights (300–18,500 g/mol) and concentrations (0–50% w/w) to modify the permeability, intrinsic crystallinity, glass transition temperature, residual solvent levels, and release of a model drug, 5-flurouracil (5FU), from monolithic films and microcapsules fabricated with PLA. The films were fabricated by solvent casting from methylene chloride. The microcapsules were formed by a coacervation method by using a methylene chloride/hexane solvent/nonsolvent system. Compared to PLA films, all PLA : PEG films showed the following: (1) a glass transition temperature between 40 and 55°C, (2) 5–8% lower residual solvent levels, and (3) enhanced permeability to 5FU. These results suggested that the incorporation of PEG improves the physical properties of PLA films to enable fabrication of controlled release delivery systems. Similar to the films, incorporation of PEG also enhanced the permeability of PLA microcapsules to 5FU. However, high intrinsic crystallinity, dual endothermal character for PLA melting, and significant burst release of 5FU in PLA : PEG microcapsules may limit their development for controlled drug delivery applications.
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Key words: biodegradable; drug delivery systems; differential scanning calorimetry (DSC); glass transition; diffusion

INTRODUCTION

Poly(lactic acid) (PLA) is a biodegradable polyester of lactic acid that was used extensively for numerous biomedical applications including the manufacture of biodegradable sutures, tracheal replacement, ligament reconstruction, surgical dressings, and dental and fracture repair.[1] The use of PLA for controlled drug delivery has potential advantages over copolymers of α-hydroxy acids (PLGAs), because its slower degradation rate minimizes accumulation of acidic degradation products that denature unstable macromolecules.[2–3] However, PLA is brittle, hydrophobic, and impermeable, as reflected in a glass transition temperature between 60 and 65°C and fractional crystallinity of up to 50%.[4–5] These physical properties limit the use of PLA for biomedical applications.

Multicomponent polymeric systems, such as block copolymers (BCPs), graft copolymers (GCPs), interpenetrating polymer networks (IPNs), and polymer-additive mixtures, were widely investigated to modify or improve physicochemical properties of individual polymers.[6–7] Block copolymeric systems of PLA with water-soluble polyethylene glycols (PEGs) have been described.[8–10] However, the effect of the physical incorporation of PEGs on PLA delivery systems was not characterized. PEGs are hydrophilic, biocompatible polymers that are available in a wide range of molecular weights (200–20,000 g/mol) and were used extensively as plasticizers for nonbiodegradable polymers such as ethyl cellulose.[11] Further, similar to PLA, PEGs are also freely soluble in methylene chloride and insoluble in *n*-hexane, a property that may enable homogeneous monolithic PLA : PEG films and microcapsules to be manufactured. We have already demonstrated that the similar solubility of PLA and PEG in nonpolar solvents can be exploited to fabricate reservoir drug delivery systems consisting of porous, degradable PLA : PEG membranes for rate control.[12] As PEG exhibits high aqueous solubility, the controlled incorporation of PEG enhanced the permeability of otherwise impermeable PLA membranes. In this research, we propose to study the effect of PEG concentration and molecular weight on the fractional crystal-

Correspondence to: D. H. Robinson (dhrobins@unmc.edu).

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TABLE I
Effect of M_W and Concentration of PEG on Thermal and Release Properties of PLA Films

Additive	% w/w	T_g (°C)	X_C	T_m (°C)	Wt. loss (%)	k (mg/h$^{1/2}$)
PLA	100	—	0.10	170.30	8.19	4.58 ± 0.17
PEG 300	10	41.35	0.09	165.92	2.80	6.47 ± 0.18
PEG 1,450	10	51.23	0.14	173.89	2.09	7.47 ± 0.29
PEG 3,350	5	50.81	0.14	174.79	2.69	7.15 ± 0.59
PEG 3,350	10	54.10	0.13	171.71	2.81	7.65 ± 1.00
PEG 3,350	20	52.18	0.13	173.75	2.15	7.86 ± 0.26
PEG 3,350	50	—	0.10	173.20	0.48	8.58 ± 2.27
PEG 8,000	10	54.82	0.07	173.46	3.17	4.22 ± 0.77
PEG 18,500	10	46.83	0.10	172.08	3.20	4.83 ± 0.14

T_g, glass transition temperature; X_C, intrinsic degree of crystallinity; T_m, weight loss; k, slope of the release versus square-root curves;—, could not be determined.

linity, glass-transition temperature, and permeability of PLA, fabricated as microcapsules and monolithic films.

EXPERIMENTAL

Materials

Poly(L-lactide) (intrinsic viscosity: 0.97 and 1.02 dL/g) was obtained from Birmingham Polymers, Inc. (AL, USA). Methylene chloride was obtained from Fisher Scientific (Pittsburgh, PA, USA), and hexane was obtained from Burdick and Jackson (MI, USA). PEG 300 was obtained from J. T. Baker Chemical Co. (NJ, USA). PEGs 1450, 3350, and 5-fluorouracil (5FU) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). PEG 8000 was obtained from Aldrich Chemical Co., Inc. (WI, USA), and PEG 18500 was obtained from Polysciences, Inc. (PA, USA).

Methods

Manufacture of PLA films and microcapsules

Placebo PLA films were prepared in stainless steel molds (60 × 30 × 5 mm) by using PEGs of molecular weights, 300, 1450, 3350, 8000, 18,500 g/mol, at 10% w/w, and PEG 3350 at 0, 5, 10, 20, and 50% w/w, for subsequent thermal analysis studies. A drying temperature of 5°C and a drying time of 48 h with vacuum drying for an additional 24 h at 35°C were used for drying the films. Drug-containing films were prepared similarly, with 5FU being dispersed in the initial polymeric solution followed by drying under conditions described above. The drug-to-polymer ratio was maintained at 1 : 1 by weight. Similarly, PLA : PEG microcapsules with and without 5FU were also prepared by using a modified coacervation-solvent evaporation method described previously.[13] Briefly, hexane (40 mL) was added dropwise to 20 mL of a 10% w/w PLA : PEG solution in methylene chloride. After stirring for 60 min to harden the microcapsule coating, the dispersion was washed thrice with 10 mL hexane, decanted, and dried under vacuum for 24 h. To encapsulate 5FU, the drug (drug : polymer ratio 1 : 1) was suspended in the PLA solution prior to the addition of hexane.

Thermal analysis

DSC thermograms were obtained by using a Shimadzu, DSC-50, differential scanning calorimeter, fitted with a Shimadzu TA-50 data processor after calibration with an indium standard (melting point, 156°C). The procedure consisted of heating ~ 2 mg samples in crimped aluminum pans at 10°C/min from 25 to 200°C in an atmosphere of nitrogen (flow rate, 20 mL/min). Changes in the glass transition temperature (T_g), melting point (T_m), enthalpy of crystallization (ΔH_c), and enthalpy of melting (ΔH_m) were measured by using TA software. The intrinsic degree of crystallinity (X_c) of each sample was calculated by using

$$X_c = \Delta H_m / \Delta H_m' - \Delta H_c / \Delta H_c' \quad (1)$$

where $\Delta H_m'$ and $\Delta H_c'$ are 203.4 and −148.5 J/g for 100% crystalline PLA.[14] This is the value reported in Tables I and II for PLA 100. For samples containing < 100%, X_c was normalized to represent only the fraction of PLA. For instance, if the measured value for X_c for PLA : PEG 3350 (90 : 10) films was 0.13, the reported value is 0.13 × 100/90 = 0.14.

Thermogravimetric analysis (TGA) was performed by using a Shimadzu, TGA-50, thermogravimetric analyzer fitted with a Shimadzu TA-50 data processor. The conditions used were similar to those described under the DSC method and consisted of heating ~ 2 mg samples in open aluminum pans at 10°C/min from 25 to 200°C. The percent weight loss for each sample was determined from Eq. 2.

TABLE II
Effect of M_W and Concentration of PEG on Thermal and Release Properties of PLA Microcapsules

Additive	% w/w	X_C	T_m (°C)	Wt. loss (%)	k (mg/h$^{1/2}$)
PLA	100	0.23	178.50	0.08	5.39 ± 0.42
PEG 300	10	0.23	175.29	0.99	7.71 ± 0.20
PEG 1,450	10	0.24	178.14	0.16	10.56 ± 0.08
PEG 3,350	5	0.21	174.91	0.65	5.52 ± 0.59
PEG 3,350	10	0.24	177.85	0.26	3.70 ± 0.08
PEG 3,350	20	0.28	177.36	0.36	11.83 ± 1.40
PEG 3,350	50	0.22	174.17	1.69	28.42 ± 0.99
PEG 8,000	10	0.21	176.67	1.06	10.35 ± 1.02
PEG 18,500	10	0.24	178.27	0.09	6.76 ± 1.48

X_C, intrinsic degree of crystallinity; T_m, weight loss; k, slope of the release versus square-root curves.

$$\% \text{ Weight loss} = 100\,(w_o - w_t)/w_o \qquad (2)$$

where w_o and w_t represent the sample weights before and after the heating cycles. Thermomicroscopic studies were also performed on all PLA–PEG samples by using a Mettler, model FP82HT, hot stage mounted on a Nikon OptiHot biological microscope with a Mettler, model FP90, central processor as the controller. All samples were heated at 10°C/min from room temperature to 200°C, and phase transitions as well as the loss of volatile components were observed by using a ×12 or ×10 objective under polarized and unpolarized light.

In vitro release of 5FU from films and microcapsules

Cumulative release of 5FU from PLA : PEG films and microcapsules was monitored by using 20 mL Sorensen's phosphate buffer, pH 7.4, in scintillation vials agitated in a horizontally shaking water bath at 5 rpm and 37°C. Five replicates of each formulation were tested. Aliquots of the dissolution media were sampled at regular time intervals, and the amount of drug released was determined by using a Shimadzu UV–visible, model 160 U, spectrophotometer at 265.7 nm. The cumulative amount of drug released was plotted as a function of the square-root of time. The modified Higuchi equation [eq. (3)] was used to interpret drug release kinetics[15]

$$Q = (2AD_{\text{app}}C_s\,t)^{1/2} \qquad (3)$$

where A is the total amount of drug in the matrix, C_S is the solubility of drug in the polymer, Q is the amount of drug released, D_{app} is the apparent diffusivity of the drug, and t is time. The slope, k, obtained from a plot of Q versus $t^{1/2}$, provides a measure of the apparent diffusivity of 5FU within the films and microcapsules and was used to compare the permeability of PLA 100 and PLA : PEG delivery systems.

Data analysis

Statistical analysis was performed by Minitab®, version 12.22, for Windows. Pearson product moment correlation coefficients ($P < 0.01$) were used to compare the relationship between the different factors and response variables measured in this study. This coefficient is used to measure the degree of linearity in the relationship between two variables and varies between −1 and +1. When one variable tends to increase as the other decreases, the correlation coefficient is negative. Conversely, a positive coefficient is obtained when two variables tend to increase together.

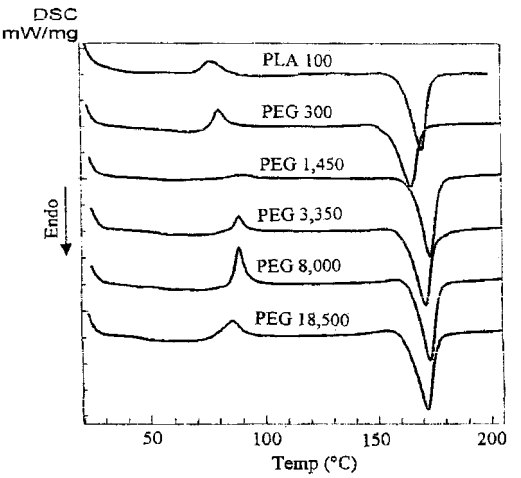

Figure 1 Effect of PEG molecular weight on DSC thermograms of PLA : PEG films.

RESULTS

Effect of PEG on the thermal properties of PLA films

Figure 1 shows the effect of PEG molecular weight on DSC thermograms of PLA 100 and those containing 10% w/w PEG. A glass transition was observed between 40 and 55°C for PLA : PEG films and was undetected in those fabricated with PLA alone. PEG 300 containing films showed the lowest T_g of 41°C and the T_g values increased with increasing PEG molecular weight, with the exception of PEG 18,500 (Table I). Following the glass transition, an exotherm was observed in the range of 70–90°C and was attributed to crystallization as confirmed by visual observation in a hot stage microscope. The correlation of this exotherm with TGA weight loss in the 70–90°C range (Fig. 5) indicated that crystallization may occur because of loss of solvent. The absence of a direct correlation between the extent of TGA weight loss and the enthalpy of crystallization suggested that other factors, such as enthalpic relaxation, may also contribute to cold crystallization of PLA. Finally, an endotherm was observed in the range of 150–180°C and was attributed to the melting of the crystalline fraction of the PLA.

Figure 2 shows that PEG melting may be detected in the range 50–60°C when the concentration of PEG 3350 in the PLA : PEG films is greater than 20% w/w. Films containing PEG also had 5–8% lower residual solvent levels than those manufactured with PLA only. Pearson's correlation coefficients (Table III) further confirmed that the percent weight loss (residual solvent levels) decreased significantly with increasing PEG concentration. Reduction in intrinsic crystallinity of PLA (X_c) was also observed in films containing PEGs 300 and PEG 8000 g/mol (Table I). Most other films showed an increase or no change in X_c.

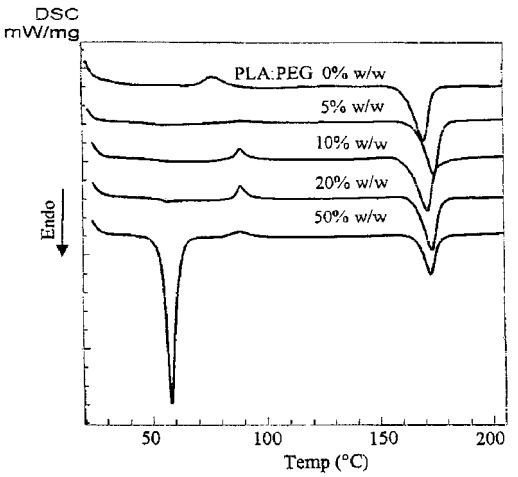

Figure 2 Effect of PEG concentration on DSC thermograms of PLA : PEG 3350 films.

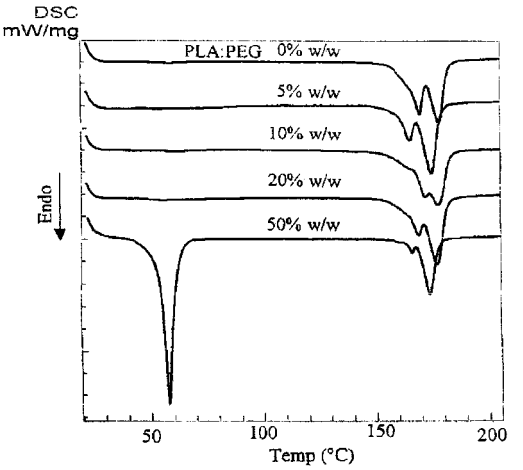

Figure 3 Effect of PEG concentration on DSC thermograms of PLA : PEG 3350 microcapsules.

Effect of PEG on the thermal properties of PLA microcapsules

Similar to PLA : PEG films, only microcapsules containing PEG concentration > 20% w/w showed PEG endotherms (Fig. 3). However, unlike films, the PLA melting peaks for microcapsules showed dual endothermal peaks, and the peak area under the first endotherm decreased with increasing PEG concentration (Fig. 3). All PLA and PLA : PEG microcapsules were also characterized by higher intrinsic crystallinities and lower residual solvent levels when compared to films of similar PLA : PEG composition (Table II). Glass transition temperatures were also not detected in the thermograms for the microcapsules of any composition. Pearson correlation coefficients showed that increasing PEG concentration significantly increased residual solvent levels ($P = 0.028$). No specific correlations were observed between intrinsic crystallinity and PEG molecular weight/concentration.

Effect of PEG on release of 5FU from PLA films and microcapsules

The rate of release of 5FU from both PLA films and microcapsules constantly declined with time (Fig. 4).

TABLE III
Effect of M_W and Concentration of PEG on Thermal and Release Properties of PLA Films and Microcapsules

Factors	Pearson coefficient	P value
PLA : PEG films		
k and PEG concentration	0.599	0.088
k and % weight loss	−0.686	0.041
% weight loss and PEG concentration	−0.666	0.050
X_c and k	0.648	0.059
PLA : PEG microcapsules		
k and PEG concentration	0.954	<0.001
k and % weight loss	0.753	0.019
% weight loss and PEG concentration	0.721	0.028

Linear regression analysis of the drug release data from both microcapsules and films using Higuchi plots [eq. (3)] resulted in R^2 values that were greater than 0.85. Pearson's correlation coefficients were also examined, and the significant correlations are listed in Table III. The values show that the release rate of 5FU increases with PEG concentration for both PLA : PEG films and microcapsules. A positive correlation was also observed between % weight loss and k for PLA : PEG microcapsules, whereas a negative correlation was observed for PLA : PEG films.

DISCUSSION

The absence of additional melting endotherms in all films and microcapsules containing <20% w/w PEG confirmed the miscibility of PEG with PLA below this concentration. The presence of a PEG melting endotherm in films containing 20 and 50% w/w PEG indicated that the solid-state solubility of PEG in PLA is below 20% w/w. These results suggest that below about 20% w/w, PEG exists as a solid-state, molecular level solution and may be used to modify the solid-state properties of PLA such as plasticity. Above 20% w/w, PEG is physically dispersed in PLA and may significantly enhance permeability. These results also correlate with release studies from films and microcapsules in that a significant increase in release rate occurred when the PEG ratio was increased from 20 to 50% w/w (Tables I and II). The negative correlation between k and % weight loss in films (Table III) can be attributed to improved packing in samples that retain higher levels of organic solvent. In microcapsules, however, the residual solvent levels are very low compared to films, and % weight loss observed on the TGA results from adsorbed moisture rather than organic solvent. This also explains the positive correla-

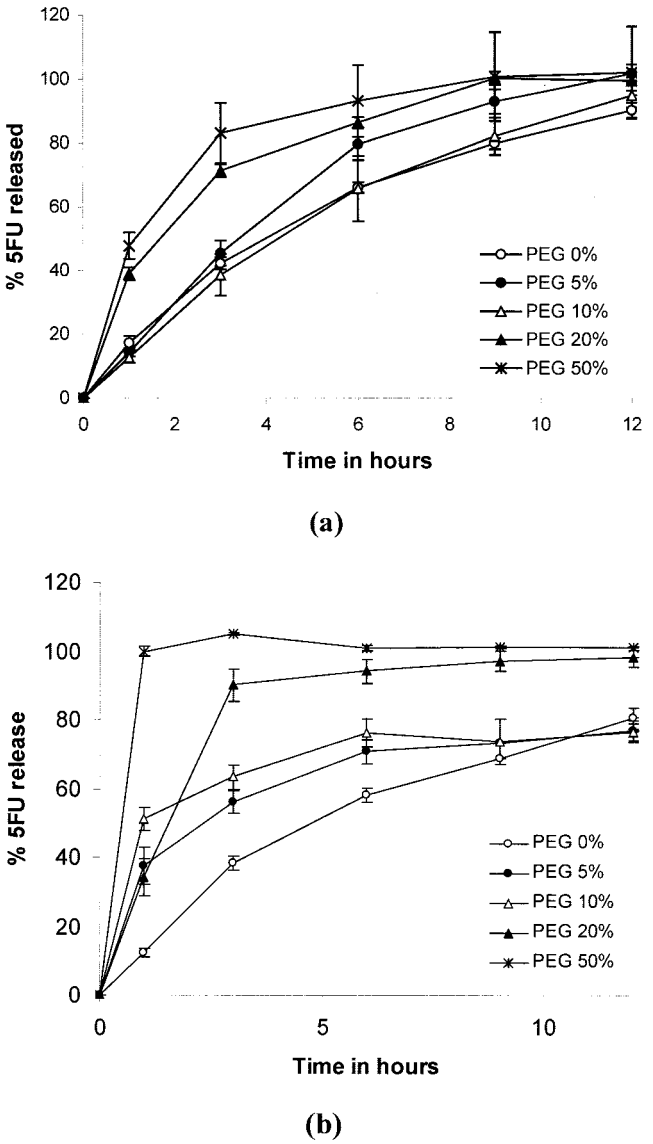

Figure 4 Representative release versus time curves, showing the effect of PEG concentration on release of 5FU from (a) PLA : PEG films, (b) microcapsules. (Values represent mean ± SEM, where $n = 5$).

tion between k and % weight loss for PLA : PEG microcapsules.

Effect of PEG on PLA films

The absence of glass transition in a semicrystalline polymer may be attributed to the impairment of intermolecular contacts between adjacent chain segments resulting in defective molecular packing resulting from disturbed parallelism of segments, growth of free volume, or mixing of polymer chains with foreign molecules.[6] Hence, the absence of a T_g in films fabricated with PLA only, and its appearance in PEG containing films, indicates that PEG improves molecular packing. The correlation of the crystallization exotherm with TGA weight loss (Fig. 5) indicates the need to minimize residual solvent levels in PLA delivery systems. As residual solvent could also be lost on storage, PLA films with high residual solvent levels may undergo recrystallization, resulting in changes in film properties. High residual solvent levels are also unacceptable as the USP limit for methylene chloride in a pharmaceutical device is 500 ppm.[16] The reduction in residual solvent levels with PEG suggests that this hydrophilic additive may potentially reduce drying times, minimize changes in physical properties during storage, and assist in gaining regulatory approval of PLA devices. The increase in intrinsic crystallinity (X_c) for films containing PEGs 1450 and 3350 in weight ratios of 300, 3500 (50% w/w), 8000, and 18,500 also correlates with improved molecular packing.

Effect of PEG on PLA microcapsules

Dual endothermal peaks for crystalline melting generally represent unstable or nonhomogeneous crystals.[6] Although PEG containing microcapsules showed a decrease in the melting enthalpy of the first melting endotherm, the dual endothermal melting could not be eliminated even in microcapsules containing 50% w/w PEG (Fig. 3). Further, the absence of a glass transition and high intrinsic crystallinity correlate with the low drug entrapment efficiency and significant burst release, because the regular structures associated with crystals are not suitable for the fabrication of spherical microcapsules. The generally low value for residual solvent levels in PLA : PEG microcapsules when compared to films, and the significant increase in these levels with PEG concentration, suggests that % weight loss in the microcapsules represents residual moisture rather than methylene chloride.

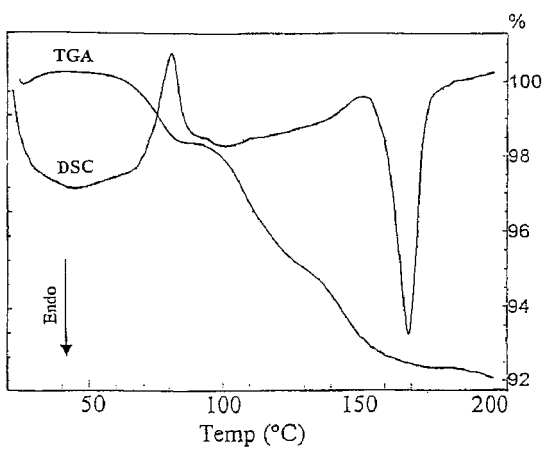

Figure 5 Representative thermograms showing the correlation between crystallization exotherms and weight loss.

CONCLUSION

This research demonstrates that the inclusion of hydrophilic, biocompatible PEGs into PLA delivery systems can modify thermal properties and drug release characteristics of both films and microcapsules manufactured using PLA. PEGs are compatible with PLA and are miscible when used below 20% w/w. Their inclusion into PLA films appears to improve molecular packing by introducing a detectable glass transition temperature and increasing fractional crystallinity. PEG also lowers residual solvent levels and enhances permeability of PLA films, thereby making it possible to fabricate PLA-based rate-controlling membranes. Compared to the PLA films, PLA microcapsules showed higher crystallinity and dual endothermic transitions for PLA melting. The incorporation of PEG reduced the dual endothermal character and also enhanced permeability of PLA : PEG microcapsules to 5FU. However, significant burst release profiles and a short duration of action make PLA : PEG microcapsules undesirable for controlled drug delivery applications.

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