Journal of Thermal Analysis and Calorimetry, Vol. 93 (2008) 1, 289–294

INVESTIGATION OF THE INTERACTION BETWEEN ACIDIC, BASIC, NEUTRAL, AND ZWITTERIONIC DRUGS WITH POLY-*L*-LACTIC ACID BY THERMAL AND ANALYTICAL METHODS

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This project investigated the interaction between poly-*L*-lactic acid (PLLA) and several therapeutic agents. Low percentage crystallinity PLLA (melt-pressed, molded and drawn) was studied. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) were used to characterize the crystallinity and thermal properties in a thermal cycling process. Repeatable melting and crystallization events were observed. The thermal properties of a drug-polymer combination using PLLA and an acidic, basic, neutral and zwitterionic material were investigated. A sufficient quantity of the drug must be present in the polymer to be observed thermally. Release of atropine sulfate from a PLLA tablet showed a two-phase process.

Keywords: *antipyrine, atropine sulfate, caffeine, crystallinity, drug release, DSC, glycine, phenobarbital, PLLA polymer-drug interaction, sulfacetamide sodium, TG, XRD*

Introduction

Poly(lactic acid) is a biodegradable and thermoplastic polymer that has been approved by the Food and Drug Administration for use in human subjects. As a biocompatible polymer, it has been employed as suture materials, inter-body cages, scaffolds for tissue engineering, and biodegradable drug delivery systems [1–3]. Poly-*L*-lactic acid (PLLA) is an optically active, semi-crystalline form of poly-(lactide) with the general formula poly-$[(O–CO–CH(CH_3)]_n$. It undergoes degradation in vivo to lactic acid by hydrolytic de-esterification [4–6]. The degree of crystallinity of PLLA influences the biodegradation rate of the polymer and can thus be modified according to its application. In vivo polymer degradation is enhanced with decreasing crystalline content. Percent crystallinity increases with increasing draw up to a draw ratio of 4. Highly crystalline PLLA is ideal for applications that require long-term mechanical and chemical stability while amorphous PLLA is suitable for applications that entail simultaneous mass loss and molecular mass degradation [4, 7–9]. In this study, low percentage crystallinity PLLA plaques prepared using different techniques were studied.

PLLA has also been utilized as a device for drug delivery. As a biodegradable polymer, it allows sustained release of therapeutic agents and eliminates the necessity of removing the polymer after the drug is spent. Proposed mechanisms for controlling drug release include Fickian diffusion, diffusion from swelling of the polymer matrix, release of drug from erosion and degradation of the polymer matrix, surface burst effect, or a combination of these mechanisms [10–12]. Interaction of the polymer with the drug is reported to affect drug release patterns. Acidic drugs are reported to increase hydrolysis of ester bonds due to acid catalysis. Basic drugs may accelerate drug release by base catalysis or suppress the release by neutralization of carboxyl end groups. Neutral drugs have weak polymer interactions due to absence of ionic interactions with the carboxyl residues [13–15]. Temperature, pH of release medium, and drug loading are also some of the factors that affect drug release [16].

In this study, six drug types were studied to represent typical therapeutic agents: salts of weak acid (sulfacetamide sodium) and weak base (atropine sulfate), acidic (phenobarbital), basic (caffeine), neutral (antipyrine), and zwitterionic (glycine) drugs. Thermal analysis of polymer-drug combinations was performed. Drug release from PLLA tablets was also investigated.

Experimental

Materials

The drugs used in the study include atropine sulfate (Ruger), sulfacetamide sodium (Spectrum), caffeine (Merck), phenobarbital (Mallinckrodt), antipyrine (Ruger) and glycine (Fisher Scientific). Structures of the drugs are shown on Fig. 1. Polymer plaques are prepared by compression molding (MOL) and melt-pressing (MP) PLLA pellets [4]. PLLA plaques are also drawn (D3) at 66±1°C with a draw ratio of

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1388–6150/$20.00

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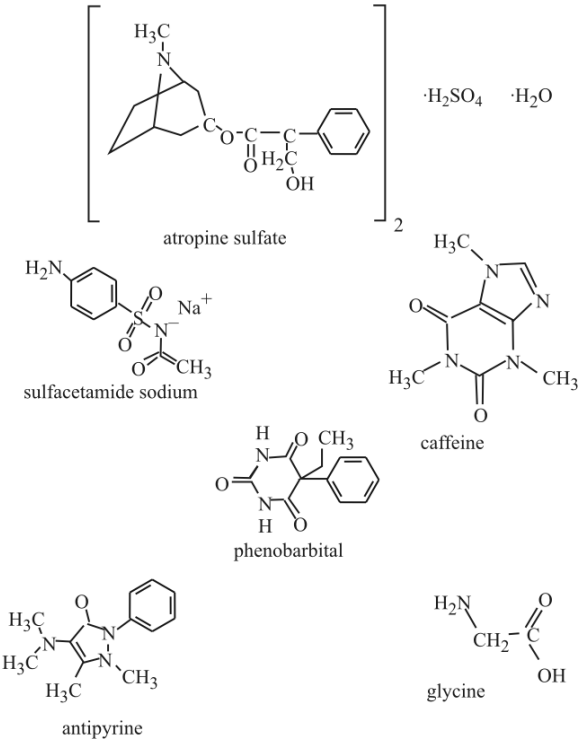

Fig. 1 Structures of drugs used in the study

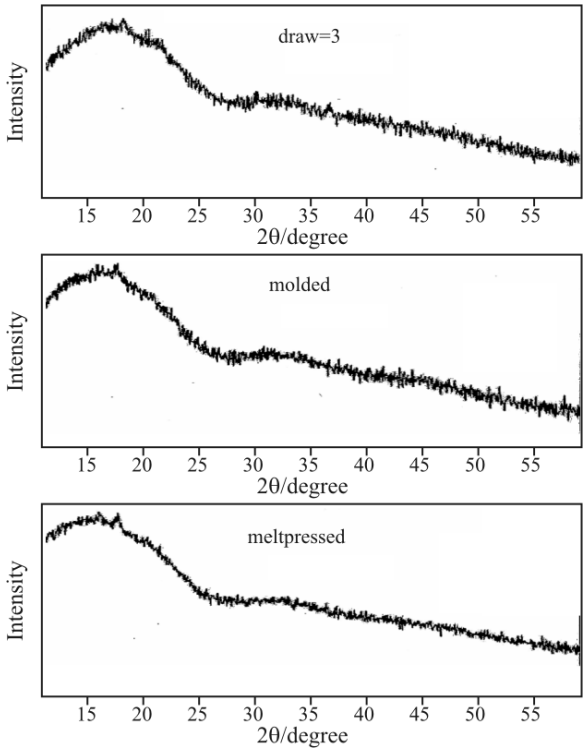

Fig. 2 X-ray diffraction data

3.0 and a draw rate of ~0.1 cm s^{-1}. Draw ratio, D, is defined as

$$D=\frac{I_f}{I_i} \quad (1)$$

Methods

X-ray diffraction

X-ray diffraction (Panalytical X-Pert Pro v.16; λ=1.54) was performed on the three types of PLLA to characterize the crystallinity of the plaques. Figure 2 shows the X-ray diffraction data of melt-pressed, molded, and drawn PLLA. Broad diffraction peaks indicate semi-crystalline behavior of the polymer. A similar XRD pattern was observed by Day *et al*. for a polylactic acid with a calculated percent crystallinity of 42.22% [17].

DSC and TG

DSC was conducted using a Mettler Toledo DSC 822[e] with a TS0801R0 Sample Robot and a TS0800GCI Gas Control calibrated with indium (melting point: 156.60°C; heat of fusion: 28.45 J g^{-1}). DSC curves were obtained using a heating rate of 10°C min^{-1} from 25 to 250–350°C with nitrogen gas (50 mL min^{-1}) and evaluated using Star[e] Software V8.10. Thermal gravimetric analysis (TG) was performed using a Mettler Toledo TGA/SDTA 851[e] with a TS0801R0 Sample Robot and a TS0800GCI Gas Control. TG curves were collected from 25–400°C at a heating rate of 10°C min^{-1} with nitrogen gas (50 mL min^{-1}) and evaluated using Stare Software V8.10. Each sample was replicated two to three times.

Thermal cycling

5 mg±1 mg of PLLA were analyzed in a heat–cool–heat–cool–heat sequence from 25–250°C. Samples were placed in 100 μL sealed aluminum pans.

Drug-polymer thermal analysis

1 mg of drug was incorporated to 10 mg of PLLA by 2 methods: placing the drug on top (top) and sandwiching the drug within fused PLLA plaques (sandwich). The prepared samples were then placed in 100 μL pans and sealed. DSC curves were obtained from 25 to 250–300°C.

Drug release study

A mixture of PLLA and atropine sulfate (20 mass/mass%) was dissolved in 10 mL methylene chloride. The solvent was evaporated and the resulting mass was compressed into a tablet (13 mm in diameter, 3 mm in height). The tablet was then immersed in a 20 mL phosphate buffer with pH 7.4 and maintained at 37°C.

Table 1 Thermal properties and percent crystallinity of different types of PLLA in a heat-cool-heat-cool-heat sequence

PLLA	Sequence	T_g/°C	T_c/°C	ΔH_c/J g^{-1}	T_{c2}/°C	ΔH_{c2}/J g^{-1}	T_m/°C	ΔH_f/J g^{-1}	χ_c
MP	heat 1	45.4	86.7	31.6	150.2	1.8	168.3	44.9	12.2
	cool 1	–	95.5	8.6	–	–	–	–	–
	heat 2	49.2	92.0	23.9	150.2	0.7	167.3	44.2	21.0
	cool 2	–	96.8	9.1	–	–	–	–	–
	heat 3	50.5	93.2	23.8	151.9	0.4	167.8	44.3	21.4
MOL	heat 1	49.2	86.2	13.0	–	–	167.0	46.4	35.6
	cool 1	–	95.3	22.8	–	–	–	–	–
	heat 2	49.4	91.0	12.3	–	–	165.0	48.5	38.7
	cool 2	–	96.8	22.1	–	–	–	–	–
	heat 3	50.8	92.2	11.8	–	–	165.8	49.7	40.4
D3	heat 1	63.1	90.0	13.4	–	–	167.2	51.2	40.4
	cool 1	–	98.6	23.5	–	–	–	–	–
	heat 2	50.2	93.4	13.9	–	–	167.7	53.4	42.2
	cool 2	–	99.8	20.8	–	–	–	–	–
	heat 3	51.5	94.5	14.7	–	–	168.4	55.1	43.1

Samples were taken at various time intervals and UV absorbance was measured at 258 nm to determine the amount of drug released.

Results and discussion

PLLA Thermal Cycling

Figure 3 shows the DSC curves obtained by thermal cycling the PLLA samples in a heat–cool–heat–cool sequence. The glass transition temperature (T_g), crystallization temperature (T_c), melting temperature (T_m), crystallization enthalpy (ΔH_c), melting enthalpy (ΔH_f) and percent crystallinity (χ_c) are listed in Table 1. Percent crystallinity is calculated using Eq. (2):

$$\chi = \left(\frac{\Delta H_f - \Delta H_c - \Delta H_{c2}}{93.6} \right) \cdot 100 \qquad (2)$$

where 93.6 J g^{-1} is the ΔH_f of 100% crystalline PLLA [18, 19].

Poly-(lactic acid) homopolymer has a T_g of 55°C and a T_m of about 175°C [20]. Malmgren *et al*. measured the T_g of a semi-crystalline PLLA to be 60°C [21]. Data show glass transition temperatures ranging from 49–64°C and melting temperatures from 165–169°C. Crystallization exotherms indicate increase in sample crystallinity. Endothermic deflection at the glass transition is due to the enthalpy stress-relaxation effect. Glass transition and post-crystallization exotherm show that the polymer contains both amorphous and crystalline regions [4, 19]. A second exotherm observed at 150–152°C for melt-pressed PLLA is due to additional crystallization in the melting region. From the data obtained, the three types of PLLA have repeatable melting and crystallization events. Percent crystallinity increases with increasing draw up to a draw ratio of 4.0 [4]. D3 exhibited the highest crystallinity while melt-pressed PLLA has the least. Crystallinity is also shown to increase during the second and third heating processes.

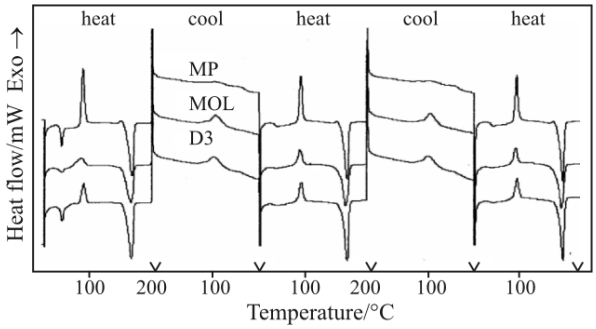

Fig. 3 Thermal cycling DSC curves of molded (MOL), melt-pressed (MP), and drawn (D3) PLLA

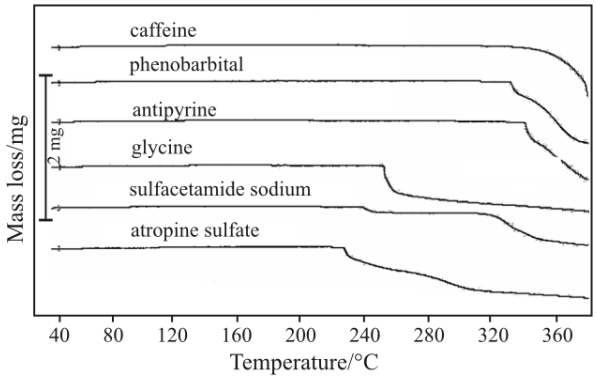

Fig. 4 TG curves of the drugs used in the study

Drug-polymer thermal analysis

DSC curves of PLLA incorporated with various drugs are shown on Figs 5a–f. The TG curves of the drugs studied are shown on Fig. 4 and verify that all of the

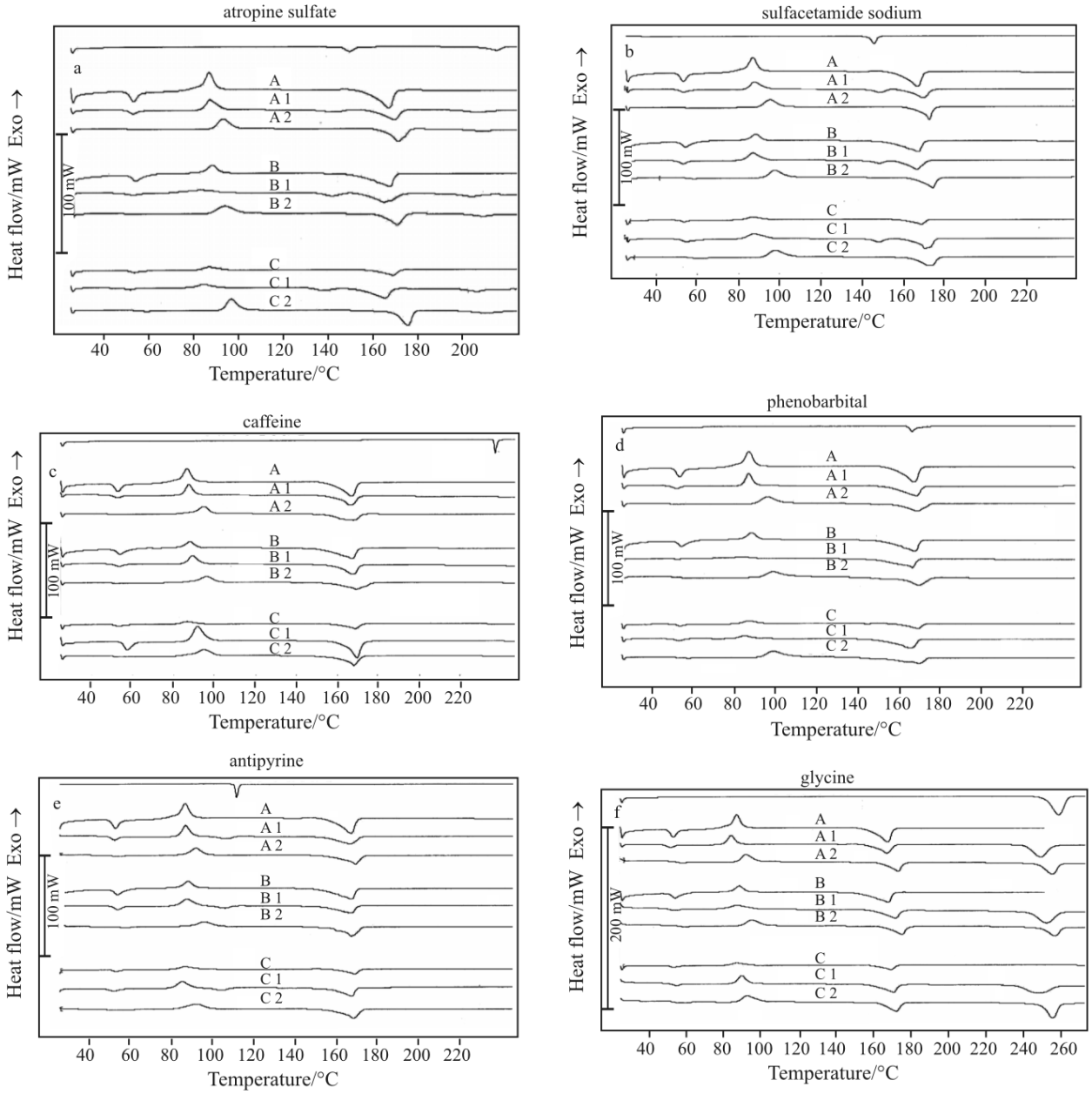

Fig. 5 DSC curves of a – atropine sulfate with PLLA (A — MP; B — MOL; C — D3; A1 — MP+drug on top; B1 — MOL+drug on top; C1 — D3+drug on top; A2 — MP+drug sandwiched; B2 — MOL+drug sandwiched; C2 — D3+drug sandwiched). b – sulfacetamide sodium with PLLA (A — MP; B — MOL; C — D3; A1 — MP+drug on top; B1 — MOL+drug on top; C1 — D3+drug on top; A2 — MP+drug sandwiched; B2 — MOL+drug sandwiched; C2 — D3+drug sandwiched). c – caffeine with PLLA (A — MP; B — MOL; C — D3; A1 — MP+drug on top; B1 — MOL+drug on top; C1 — D3+drug on top; A2 — MP+drug sandwiched; B2 — MOL+drug sandwiched; C2 — D3+drug sandwiched). d – phenobarbital with PLLA (A — MP; B — MOL; C — D3; A1 — MP+drug on top; B1 — MOL+drug on top; C1 — D3+drug on top; A2 — MP+drug sandwiched; B2 — MOL+drug sandwiched; C2 — D3+drug sandwiched). e – antipyrine with PLLA (A — MP; B — MOL; C — D3; A1 — MP+drug on top; B1 — MOL+drug on top; C1 — D3 + drug on top; A2 — MP + drug sandwiched; B2 — MOL + drug sandwiched; C2 — D3+drug sandwiched). f – glycine with PLLA (A — MP; B — MOL; C — D3; A1 — MP+drug on top; B1 — MOL+drug on top; C1 — D3+drug on top; A2 — MP+drug sandwiched; B2 — MOL+drug sandwiched; C2 — D3+drug sandwiched)

volatile processes are >230°C and did not interfere with the DSC analysis. In order to obtain a reliable DSC curve, the sample should be in good contact with the sample pan [22]. Melting endotherms of the drugs were observed on the DSC curves of PLLA incorporated with such drugs. This indicates that the drug should be present in the polymer for it to be observed thermally. ΔH_f values of the polymer range from 39–50 J g^{-1}. Drugs (antipyrine and sulfacetamide sodium) that melt below the melting temperature of the polymer were not

observed on the curves of the polymer-drug combinations which utilized the sandwich method. Also, only the second endotherm of atropine sulfate was observed using the sandwich method. Phenobarbital which melts at 165°C has a melting endotherm that is superimposed with that of the polymer. The melting enthalpies of the polymer in combination with phenobarbital show larger values (47–62 J g^{-1}) when compared to other drug combinations. This proves that the melting enthalpy of phenobarbital was included in the polymer endotherm. Caffeine melting endotherms were not observed with any of the polymer-drug combinations. Amorphous caffeine was suspected to form such that no melting peak was observed. Crystallization temperatures and enthalpies using the top method were lower than those prepared by the sandwich method. Endothermic deflection at the glass transition temperature due to stress relaxation effect was minimized with the sandwich method. PLLA has undergone a first melting process during the sandwich method sample preparation. Its thermal properties for the drug-polymer combination is therefore comparable to the second heating sequence (Fig. 3) which showed an increase in crystallization temperatures and a minimization of the stress relaxation at the glass transition. DSC has been utilized as a tool to investigate drug-excipient interactions. The thermal curves of individual substances are compared to the thermal curve of the mixture. The latter should show a summation of the thermal properties of the two substances investigated. An interaction is shown to occur if there are changes in transition temperature, peak area and shape, and the appearance or disappearance of peaks. However, changes in temperature or peak shape and area usually arise from mixing the components. Therefore, it is generally concluded that provided all thermal features are shown in the thermal curve of the mixture and no appearance of new peaks are observed, then the components have no interaction [23–25]. Melting endotherms of all drugs tested, except caffeine, were seen in the drug-polymer thermal curve. Slight broadening of the drug peaks and lowering of the melting temperatures can be attributed to mixing with the polymer. Based on the criteria above on how interactions are evaluated by DSC, these drugs showed to have no interaction with the polymer.

Drug release study

A two-stage drug release profile was reported by Miyajima *et al*. [26–28] for the release of basic, acidic and neutral drugs from PLLA rods. The first release stage was due to diffusion through the hydrated matrices of amorphous PLLA. When PLLA transformed to a semicrystalline state at the second release stage, diffusion through water-filled micropores allowed the drugs to diffuse from the rods. The transformation of PLLA from amorphous to semicrystalline is reported to induce the transition between the two release stages, with the release rate slower in the first stage than in the second stage.

Gallagher and Corrigan [12] also reported a biphasic release of drug from biodegradable polymers, with the initial release or 'burst' phase resulting from rapid dissolution of the drug at the solid–liquid interface followed by a polymer degradation phase. A proposed model Eq. (3) describes the fraction of drug released over time. The total fraction of drug (F_{TOT}) released at time t is equal to the sum of drug released by surface diffusion and that released by degradation of the polymer matrix:

$$F_{TOT} = F_B(1-e^{-K_B t}) + (1-F_B)\left(\frac{e^{kt-kT_{max}}}{1+e^{kt-kT_{max}}}\right) \quad (3)$$

where F_B is the fraction of the drug load released in the burst phase, K_B is the release rate constant during the burst phase, k is the rate constant in the polymer degradation phase, and T_{max} is the time to maximum drug release rate.

Sigma Plot Version 10.0 was used to fit the model equation above to the data. The fitted curve is shown on Fig. 6 and the estimated parameters are listed on Table 2. Atropine sulfate was used as the model drug for this study. Approximately 50% of the drug is released after 50 h and almost 100% at 140 h. A two-stage process can be observed from the data, with the initial rapid release reaching a plateau at 40–60 h.

Table 2 Estimated parameters for the release of atropine sulfate from PLLA tablets

F_B	0.7569±0.1377
K_B/h^{-1}	0.0207±0.0063
k/h^{-1}	0.1170±0.1096
T_{max}/h	112.6234±5.9030
R^2	0.9800

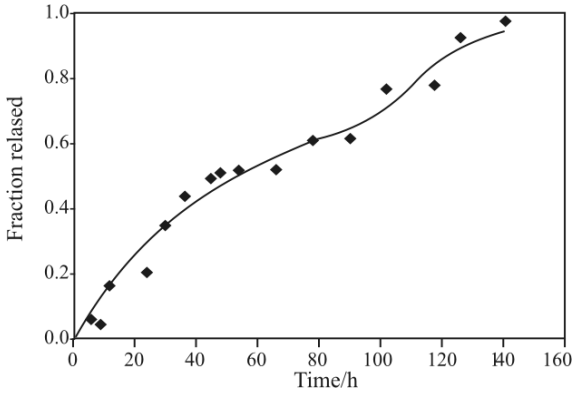

Fig. 6 Release profile of atropine sulfate (20 masss/mass%) from PLLA tablets maintained at 37°C

The sharp increase in the second stage may be brought about matrix degradation. From the calculated parameters obtained from Eq. (3), approximately 76% of the drug is released after the burst phase with a rate constant of 0.02 h^{-1}. The release rate of the polymer degradation phase is faster with a rate constant of 0.1170 h^{-1} and the time to reach maximum drug release rate is 112 h.

Conclusions

Thermal cycling of PLLA shows repeatable melting and crystallization events. Drawn PLLA exhibited the highest crystallinity while melt-pressed PLLA showed the lowest crystallinity. Percent crystallinity is also shown to increase during the second and third heating processes. The melting endotherms of the drugs were observed on the DSC curves of polymer-drug combinations which indicate that the drugs should be present in the polymer to be observed thermally. Antipyrine and sulfacetamide sodium which have melting points below that of the polymer were not observed on the curves of the polymer-drug combinations prepared by the sandwich method. Only the second melting endotherm of atropine sulfate which has a higher T_m than the polymer was observed using the sandwich method. Phenobarbital which melts at 165°C has a melting endotherm that is superimposed with that of the polymer. Caffeine melting endotherms were not observed with any of the polymer-drug combinations. The crystallization temperatures and enthalpies using the sandwich method were higher compared to those prepared by the top method. All drugs, except caffeine, when combined with the polymer showed thermal curves which were a summation of the individual curves of the drug and the PLLA. These drugs therefore exhibited no interaction with the polymer. Absence of caffeine melting peak in caffeine-PLLA curves is suspected to be due to the formation of an amorphous form of the drug. Drug release of atropine sulfate from PLLA tablet showed a two-stage release process with the release rate of the second stage being higher than the initial phase. Approximately 98% of the drug was released after 140 h. Based on Gallagher and Corrigan's model equation, approximately 76% of the drug was released after the initial burst phase.

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DOI: 10.1007/s10973-007-8836-7