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RESEARCH PAPER

In Vitro Release of Theophylline from Poly(Lactic Acid) Sustained-Release Pellets Prepared by Direct Compression

A. Kader* and R. Jalil

Faculty of Pharmacy, Dhaka University, Dhaka 1000, Bangladesh

ABSTRACT

Poly(L-lactic acid), (L-PLA) pellets containing theophylline as a model drug were prepared with increasing bovine serum albumin (BSA) load of 10, 20, 30, 40, or 50% by direct compression. The drug release from pellets was studied in phosphate buffered saline (PBS, pH 7.4) at 37°C. The annealing effect on theophylline release from pellets was also studied at 20, 30, 60, and 80°C. In all cases, release kinetics followed the Higuchian mechanism with an initial burst effect followed by sustained release of theophylline during the experimental period. Increasing BSA load resulted in a linear increase in Higuchian release rates presumably because of the hydrophilic nature of BSA. Furthermore, BSA did not interact chemically with the polymer matrix and was held physically by the dense polymer matrix. However, drug release decreased with an increase in annealing temperature. Release of theophylline was higher from PLA–BSA combination pellets compared to PLA pellets at temperatures below the glass transition temperature (T_g) of the polymer and lower for temperatures above T_g. The temperature effect on drug release may be attributed to both the reduction of core solubility in the bulk phase and the lowering of diffusibility of the polymeric membrane. No drug–polymer interactions or polymer degradation was observed within the experimental setup when studied by differential scanning calorimetry (DSC), infrared (FTIR) spectroscopy, and gravimetric methods. DSC studies of pellets showed no hints of microstructural changes (crystallinity) of the polymers. In our experiments, theophylline was released primarily by leaching through channels and not by polymer degradation. The release rate was dependent on BSA loading and annealing. It may be concluded that PLA pellets can be fabricated suitably using BSA and annealing to design sustained-release preparations of water-soluble drugs.

*To whom correspondence should be addressed. Guilford Pharmaceuticals, Inc., 6611 Tributary St., Baltimore, MD 21224. Fax: (410) 631-6848. e-mail: Kader_A@guilfordpharm.com

INTRODUCTION

Over the last two decades there has been an overwhelming interest in the use of lactic acid homo- and copolymers as biodegradable matrices for controlled drug delivery systems and at least one implant (Zoladex®, ICI, UK) and two injectable microsphere products for a 1-month period (Decapeptyl®; Ipsen Biotech, France, and Parlodel®, Sandoz, Switzerland) are currently on the market (1–3). A number of fabrication techniques such as film casting, extrusion, molding, microencapsulation, and spray-drying have been applied to the preparation of poly(lactic acid) (PLA) dosage forms. However, these methods can be time consuming, dependent on many parameters, and most importantly difficult to scale up for large-scale manufacturing. The direct compression method was found to be easy to scale up and less complicated when compared to other methods (4). The drug release from PLA polymers is complicated by their degradation and erosion (5). It is important to accumulate information related to the release kinetics from this polymer if dosage forms for clinical applications are to be prepared using these biodegradable polymers as a drug carrier matrix.

Nondegradable polymers have been used extensively in oral dosage forms to sustain drug release. However, unwanted intestinal retention of the nondegradable polymeric material may occur upon chronic dosing. Biodegradable polymers have been suggested for use in oral, controlled drug delivery systems to avoid polymer retention in the intestine or to avoid surgery to remove nondegradable implants. The polymers currently designed to deliver drug(s) release the drug so slowly that they are unsuitable for oral use (6). The rate of biodegradation is a function of molecular weight (MW) and can range from weeks to months (3,7). The rate of aqueous degradation of the polymer may be influenced by physiological variables. To overcome the variability of degradation and/or erosion, we used very high MW PLA polymer. Common techniques for polymer fabrication often use heat which may influence release kinetics from the pellets. A low MW water-soluble drug, theophylline, was chosen as the model drug in these studies. The narrow therapeutic range and the short half-life of theophylline (±6 hr) require repetitive daily administration of a conventional formulation (8). Sustained-release (SR) formulations improve patient compliance and decrease the plasma concentration fluctuations. In these studies, we have made pellets by direct compression using very high MW PLA for sustained release over 2–4 days. The release of theophylline was modulated by different factors such as compression pressure, loading of a water-soluble compound in the pellets, and temperature and time of annealing. These pellets could be used as either implantable or oral dosage forms.

EXPERIMENTAL SECTION

Materials

Poly(L-lactic acid) (L-PLA, viscosity average MW = 61,300, glass transition temperature [T_g] 66.5°C, melting temperature [T_m] 100°C, Boehringer Ingelheim, Germany; bovine serum albumin (BSA), theophylline, and all other chemicals were from BDH, England.

Pellet Preparation

The polymer L-PLA was dissolved in acetonitrile with mild heating and ultrasonication. After cooling, BSA was added gradually with constant stirring and the solution was dried under a stream of cold air. Final drying of the mixture was done in a vacuum desiccator over silica for 24 hr prior to drug incorporation. The formulation of the pellets is shown in Table 1. Theophylline was mixed with the dispersed polymer mass (drug:polymer 1:4) and blended in a mixer for 30 min. One hundred milligrams of the solid dispersed mass was compressed on a Perkin-Elmer hydraulic presser (Germany) with 2 tons pressure (15 kN/cm^2) (flat-faced punch–die set). For each batch, 3–5 pellets (13 mm diameter) were prepared to study theophylline release kinetics in triplicate and stored in a desiccator.

Pellet Annealing

Initial weights of the pellets (n = 5) were accurately measured and numbered. These pellets from each batch

Table 1

Formulation of PLA–BSA Pellets Containing Theophylline

Batch	L-PLA:BSA	Theophylline Content (%)	Mean Pellet Weight (mg)
A	100	20	97
B	90:10	20	97
C	80:20	20	102
D	70:30	20	104
E	60:40	20	104
F	50:50	20	103

were heated at 30, 60, or 80°C in a hot-air oven for 15 min. The samples were cooled before set for the drug release study.

In Vitro Drug Release Study

Initial weights of the pellets (n = 5) were accurately measured and numbered. The weight variation (coefficient of variation [CV] 1.1%) was evaluated for the pellets on an electronic balance. The friability of the pellets was also determined in a friability tester (Erweka TA 3R, 15 min, 20 rpm, CV 2.0%). Each of the pellets was placed in a 100-ml Erlenmeyer flask filled with 100 ml phosphate buffered saline (PBS, pH 7.4) and incubated at 37°C in an incubator (Memmert, Germany). Five milliliters of the sample was withdrawn from each flask and replaced with fresh PBS with an appropriate time interval for 5 days to maintain a sink condition and samples were assayed spectrophotometrically at 270 nm using a Pye-Unicam SP8-400 spectrophotometer (England). The CV of the release data was smaller than 10%. The polymers did not interfere with the assay. To detect potential drug degradation during the release study, physical mixtures of drug and polymer were run. No changes in absorbance or UV profiles were noted over the time periods investigated.

Measurement of Pellet Erosion and Swelling

Measurements of matrix erosion and swelling were carried out on the pellets containing no drug. Six pellets (mass = X) were placed in the dissolution apparatus and subjected to the conditions used in the dissolution test described above. Each basket was taken out at predetermined time intervals, excess water was removed, and the basket placed on a small aluminum pan, allowed to stand for 3 min at room temperature (21°C), then weighed (mass = Y) and dried at 80°C to a constant weight (mass = Z). These three weights give the initial dry weight (X), the wet weight after being immersed in water for a given time interval (Y), and the corresponding dry weight (Z); weights Y and Z including that of the dry basket and small aluminum pan. The diameters of the matrices were also measured immediately after samples were taken out of the dissolution medium.

If DB is the weight of a dry basket and small aluminum pan, matrix erosion and water uptake can be expressed, in percentage, as

$$\text{matrix erosion} = [X - (Z - DB)] \times 100/X$$

$$\text{water uptake} = (Y - Z) \times 100/(Z - DB)$$

Differential Scanning Calorimetry (DSC)

The DSC of the pellets was studied using a differential scanning calorimeter (Perkin-Elmer, Norwalk, CT). Samples (10–20 mg) were weighed and crimped into aluminum pans. Samples were examined at maximum sensitivity from 35 to 80°C to determine glass transition temperatures (T_g). Samples were heated from -5 to 185°C at 20°C/min and then quenched to -5°C. They were then reheated under the same conditions. The T_g values and their associated energies of transition are given in Table 2. The system was calibrated using an indium standard. An average of three determinations was made for each polymer sample.

Infrared (IR) Absorbance Spectroscopy

The IR absorption spectra were determined with a Pye-Unicam SP3-100 spectrophotometer over the range 4000–400 cm^{-1} with a scan time of 3 min. Potassium bromide disks (100 mg, 1% polymer) were compressed under reduced pressure.

RESULTS AND DISCUSSION

The biodegradable polymer selected for the preparation of the pellets was a high MW L-PLA. L-PLA meets the requirements needed from a matrix for drug delivery applications including suitable mechanical properties, biodegradability, tissue compatibility, and ease of processing. L-PLA was easily compressed into pellets with high compression pressure. The use of a high MW polymer should produce high internal void volume compared to a low MW polymer at the same compression pressure. The compressibility of a low MW polymer is higher than that of a high MW polymer. L-PLA is ex-

Table 2

Thermal Glass Transition Temperatures (T_g) and Heats of Transition of PLA Samples[a]

Batch	T_g (°C)	Heats of Transition (cal/g)
A	65.8	1.5
B	65	1.51
C	64.5	1.46
D	63	1.63
E	64.8	1.52
F	63.5	1.53

[a]All values were mean of three determinations with %CV less than 10.

pected to be chemically stable at 25°C for up to 120 days (2). This makes the high MW polymer suitable for our investigation. We were interested in modulating drug release from this polymer without its degradation and erosion. The high internal void volume of this polymer should enhance drug release from the pellets by leaching or simple diffusion. Theophylline was used as model drug because of its stability and ease of analysis and its comparable solubility in water, PBS (pH 7.4), and normal saline (data not shown).

BSA has a high MW and is water soluble, and unlike L-PLA, it should enhance drug release of a water-soluble compound in an aqueous medium. We have investigated the use of BSA in L-PLA pellets to modulate release of theophylline at a constant or biphasic release rate over several days. In addition, the effect of annealing on the release kinetics was also investigated.

Effect of BSA Loading

All pellets were made with 2 ton compression pressure as described. An increase in compression pressure was found to decrease drug release from pellets (data not shown). The prepared pellets were easy to handle because of high mechanical strength and almost complete lack of friability. Pellets were prepared with an increasing BSA load of up to 50% (Table 1). Under physiological pH values in the dissolution medium, L-PLA matrix tablets gave sustained release of incorporated theophylline (Fig. 1). The influence of pH on drug release from these pellets has also been described (unpublished results).

For the mixed hydrophobic/hydrophilic matrix system under investigation, drug release involves (*a*) penetration of the solvent into the matrix, (*b*) hydration and swelling of the polymer and dissolution of the active ingredients, and (*c*) transfer of the dissolved drug and soluble components into the bulk (7). Because of its chemical stability, its swelling because of water penetration was negligible.

The release of theophylline from the pellets was found to be biphasic, with an initial large and fast release followed by a much slower release (Fig. 1). The figure shows release profiles of theophylline from L-PLA tablets with 10–50% BSA loading in PBS. Theophylline release from these pellets depends on BSA loading of the matrix. Release kinetics could be described with the well-known Higuchi equation (9):

$$Q = 2C_0 (Dt/3.14)^{1/2}$$

where Q is the amount of the drug released per unit area (cm^2), C_0 is the initial quantity of the drug (mg), D is the diffusion coefficient, and t is the time after application (hr). Because C_0 and D are essentially constants, the equation can be reduced to

$$Q = k' t^{1/2}$$

where k′ is the constant or the Higuchi release rate constant. The data were then treated with this above equation, and the percent theophylline released (Q) was plotted against the square root of time ($t^{1/2}$) (Fig. 2). The given parameters were calculated after linear re-

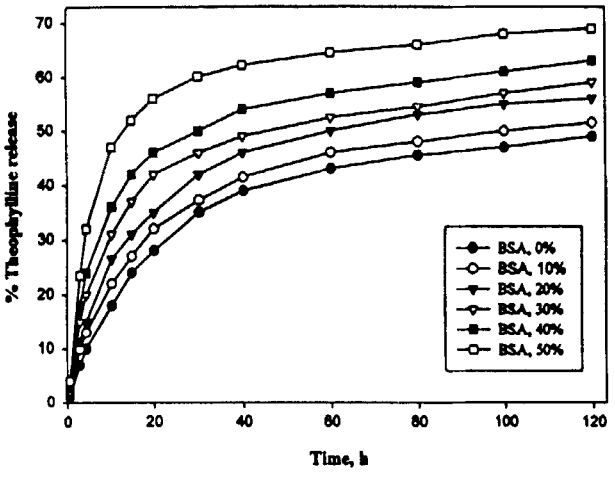

Figure 1. Effect of BSA loading on the release of theophylline from PLA pellets. All values were the mean of at least three determinations with %CV less than 0.1.

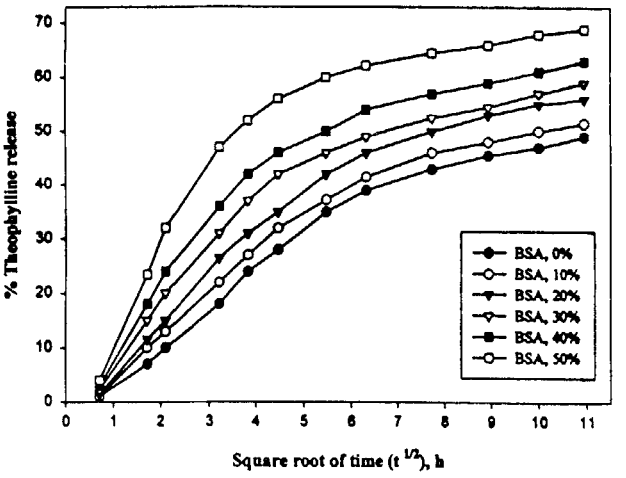

Figure 2. Higuchi plot of theophylline release from PLA pellets from Fig. 1.

gression analysis and an excellent linearity was found, confirming that the release permeation data followed the Higuchi model ($R > 0.07$). Extrapolation of the first linear portion of the Higuchi plot showed a negative value on the time axis, indicating the presence of an initial rapid release rather than a lag phase. But with no BSA load and even with 10% BSA load, a lag phase was observed (positive values upon extrapolation). This small lag time was required presumably for the initial wetting, and penetration of dissolution medium into the matrix prior to a delayed release was obtained. The first-order plot of the release data showed large variations in the extent of linear portions of the curve, indicating that the drug release was not first-order (data not shown). The Higuchian release of theophylline from each pellet was calculated from the slope values of the straight lines from Fig. 2. Figure 3 shows a linear increase in the Higuchian release rate with an increase in BSA concentration. This is in full agreement with the Fickian diffusion kinetics of small molecules from a matrix into the dissolution fluid.

The initial phase of release was very rapid and the quantity of the drug released increased with an increase in BSA loading. The quantity of theophylline released in this phase was due to greater extraction of theophylline from the vicinity of a pellet surface, where wetting and dissolutions take place from a very large surface area. In the absence of BSA, the hydrophobic nature of PLA impedes wetting and penetration of dissolution fluid, which leads to a leaching of the drug from the pellet. Release during this phase was mainly from the surface. This initial burst effect could be reduced by the complete removal of the drug from the surface. Also, upon storage of the pellets, this initial burst effect diminished (data not shown).

In this study, the initial effect was also much more prominent with increasing BSA loads. Since BSA solubility in the polymer is negligible, diffusional transport of the agent through the polymer phase is not efficient. As expected, 10% BSA load did not show much drug release where the 50% BSA load acts itself as a matrix for the drug which is soluble in the release medium. The aqueous solubility of both BSA and theophylline is responsible for increasing percentage release of theophylline with an increase in BSA loads. Also, BSA was expected to act as a surfactant. After the initial release, the release rate was dominated mainly by leaching of the drug from the matrix through the pores formed during initial drug release. Since polymer degradation for a 5-day period has been insignificant, diffusion of the drug by polymer degradation could not be considered.

Annealing Effect

Annealing temperatures ranging from 20 to 80°C were used to study the release properties of theophylline in PBS. The PLA and PLA–BSA combination pellets containing theophylline have been found to follow a Higuchian release mechanism. The release data from PLA and PLA–BSA pellets at different temperatures are shown in Figs. 4 and 5, respectively. These show that variations of annealing temperature do not change the

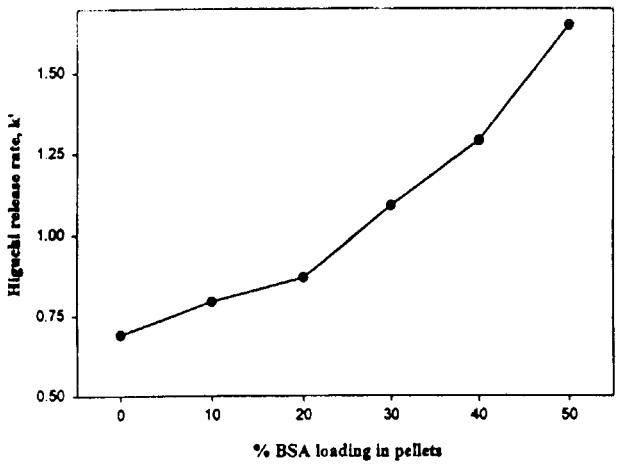

Figure 3. Effect of BSA loading on the Higuchian release rate constant (k') of theophylline from PLA pellets (see also Fig. 1).

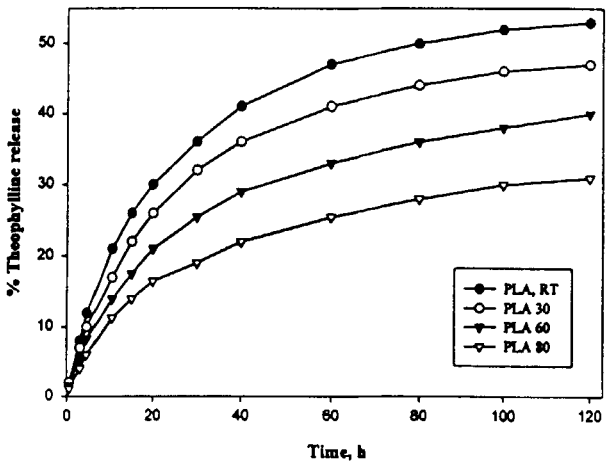

Figure 4. Effect of annealing on the release of theophylline from PLA pellets. All values were the mean of three determinations with %CV less than 0.1.

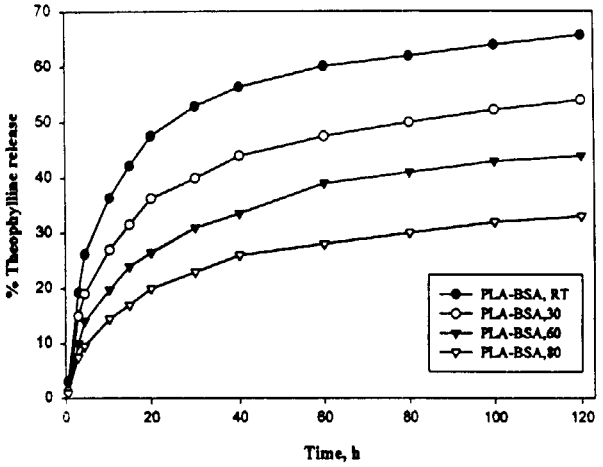

Figure 5. Effect of annealing on the release of theophylline from PLA–BSA combination pellets with 50% BSA loading. All values were the mean of four determinations with %CV less than 0.1.

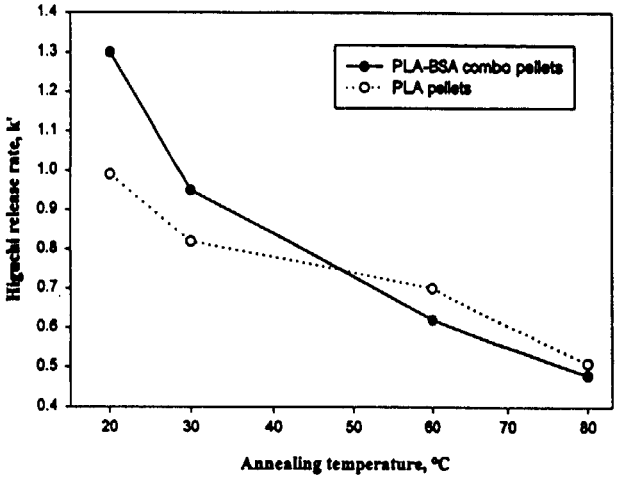

Figure 6. Effect of annealing on the Higuchian release rate constant (k′) of theophylline from PLA or PLA–BSA combination pellets. Values were derived from Figs. 5 and 6.

release pattern after an initial burst effect and a subsequent lag phase. Pellets prepared from L-PLA also showed a similar release pattern with a lower drug release rate compared to PLA–BSA combination pellets. At low temperature, i.e., 30°C, theophylline release from pellets was not very prominent. But at higher annealing temperatures, the initial rapid release effect and subsequent lag phase are significantly affected by a much lower drug release. The quantity of theophylline released during the initial phase was reduced at higher temperatures with all pellets, which was attributable to the lower extraction of theophylline from the vicinity of the pellet surface as the temperature increased. The incorporation of BSA in the matrix disks had the same effect with increasing temperature. Because of protein aggregation at higher temperature, leaching of the drug from the PLA–BSA pellets would be expected to be less. Indeed, the effect of temperature on the BSA was much more prominent with 40% BSA load and the release rate at 80°C was comparable to that of the L-PLA.

Variations in annealing temperature caused changes in the Higuchian release rate and $T_{50\%}$ (Fig. 6). Increased temperature decreased the intrinsic diffusibility because of the thermoplastic nature of the polymer (10). At 80°C, which is above the T_g of the polymer, drug release was significantly affected because of its effect on free volume, permeability, and chain mobility (11). Annealing of polymers often influences these mechanical properties of the polymer (12,13). In general, annealing decreases the density within the polymer and improves the dimensional stability by raising the modulus. Slow cooling of an annealed polymer also tends to remove any residual stress, strain, or defects that may have occurred during processing. Thermal treatment may also have contributed to improving the bonding strength by increasing the polymer modulus, as well as removing any defects which could have disturbed the structural integrity of the polymeric network throughout the matrix. The pellets were thermally treated to temperatures above and below the T_g of the PLA. The results of the dissolution studies showed that thermally treating the pellets to temperatures above the T_g of the PLA significantly retarded the matrix drug release compared to pellets which were not thermally treated. The retardation in drug release could be attributed to a stronger compact and a more efficient redistribution of the polymer throughout the tablet matrix, based on fundamental principles of annealing.

Three heating temperatures were chosen relative to the T_g of the pure PLA (T_g = 57°C). Thermal treatment at 40°C represents heating temperatures below the T_g of the PLA, and thermal treatment at 60 and 80°C represent heating temperatures above the polymer T_g. Pellets that were preheated at 40°C showed a small reduction in the drug release as compared to nonthermally treated tablets. However, pellets treated to 60 and 80°C showed much larger reductions in the release of theophylline. Furthermore, the time of heating was also investigated up to 12 hr. It was found that the longer the duration of thermal treatment, the greater the retardation of drug

release when compared with the nonthermally treated tablets (unpublished results).

Compaction studies demonstrated that the thermally treated pellets were significantly harder than the nonthermally treated pellets. These results suggest that thermal treatment increases the binding capacity within the tablet, resulting in a slower release rate of the drug from the pellet, especially above the T_g of the polymer. Results from tablet index testing supported the dissolution results. The bonding index of the compact formulations increased after thermal treatment above the T_g of the PLA (data not shown).

Pellets, which were heated above T_g of the polymer, exhibited smoother surfaces when compared to other pellets under the light microscope (data not shown). These results could be attributed to the thermochemical behavior associated with the T_g. Heating the pellet to temperatures above the T_g of the polymer promoted polymer chain movement, which resulted in a better redistribution of the polymer throughout the matrix after cooling. Overall, this process resulted in a reduction in the diffusion and the rate of the drug released. As seen by the profiles using the Higuchi relationship, thermal treatment reduced the rate constant (k', slope) by approximately 20% for each formulation as compared to nonthermally treated pellets.

Pellet Stability

Any change in the polymer was monitored by the gravimetric method (pellet degradation and erosion) and IR spectroscopy. The IR spectra of the samples were identical irrespective of BSA loading or annealing. The major absorbance peaks are concomitant with the assigned structure of lactic acid, namely, 2900–2800 (C–H stretch), 1750 (C = O anhydride), 1300–1000 (C–O stretch), 950–700 (C–H bend) cm^{-1}. No absorbance band at 1600 cm^{-1} regions was observed when the pellets were analyzed before and after the experiment. Placebo pellets were exposed to the medium, dried, and then analyzed. No extra band was observed, indicating the absence of any ionized carboxyl groups which may be generated from polymer degradation (Fig. 7).

Visual or light microscopic observation of the pellets during the course of the release study revealed that the pellets (batch A) did not swell nor did they erode away (data not shown). Less than 50% theophylline was released from the PLA pellet, in absence of BSA, which eliminated any possible degradation of L-PLA. The pellet did not change in size. This drug release from this matrix could be explained because of the very high MW

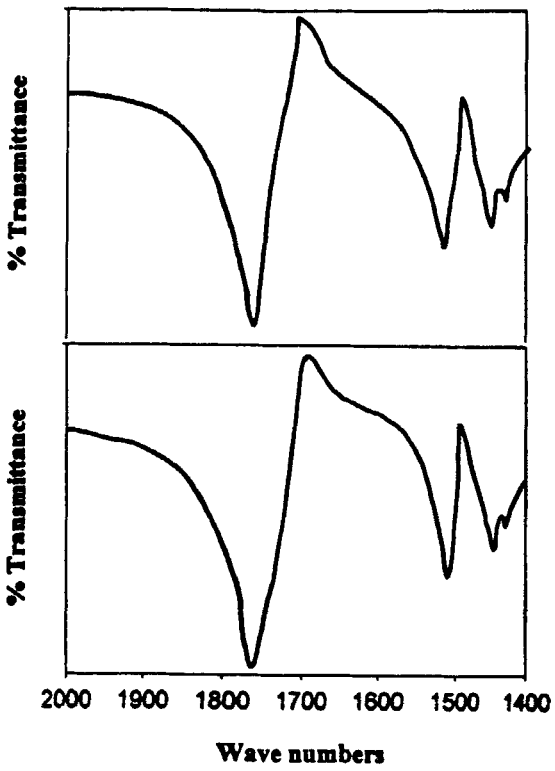

Figure 7. Selected range of IR spectra of L-PLA before (a) and after (b) drug release studies. Note that there is no band around 1700–1550 cm^{-1}, indicating no degradation of the polymer.

of the polymer. The end groups of the polyester and PLA are hydroxyl and carboxyl groups, respectively. The end group:polymer chain ratio increased with decreasing MW (14). The number of carboxyl groups was therefore significantly low in L-PLA. The hydration of the pellets (batch A) was studied as a function of dissolution medium and was found to be insignificant (5.5%). Ionization of the carboxylic end groups in the polymer was the primary driving force for swelling and hydration of the low MW PLA. The number of carboxyl groups in L-PLA pellets was not sufficient to cause pellet hydration. In addition, these semicrystalline L-PLA (T_g = 65°C) was in the glassy state at 37°C.

DSC Studies

DSC was conducted on pure PLA samples after thermal treatment in order to investigate possible changes in the T_g that may have occurred (10). The T_g of the polymer samples did not demonstrate any significant changes after thermal treatment (Table 2). In addition to pure

polymers, pellets from both thermally and nonthermally treated pellets were also tested using DSC. Thermal treatment had no effect on the T_g in pellet samples containing the PLA. The results showed that the T_g of pellets was unchanged compared to the T_g of the pure polymer sample. T_g was unaffected by thermal treatment. In addition, the T_g of the pure PLA was not influenced by combining the polymer with the other formulation components such as BSA or by processing conditions such as annealing used in pellet fabrication. Similar results were obtained by other groups (12,13). DSC results also suggest that theophylline and/or BSA did not interact with the polymer to an extent that would influence the transition enthalpy. We speculated that BSA was held physically by the dense polymer matrix, as suggested earlier (15).

CONCLUSIONS

The drug release from polymeric matrix systems depends on factors such as drug loading, release media, the physicochemical properties of the drug and the polymer, and physical factors such as temperature. The BSA loading into pellets and pellet annealing affect drug release kinetics from the pellet. These techniques could be used as effective means of modulating drug release parameters. The drug is released primarily by leaching through channels. In this study, the pores and channels created by dissolved drug particles were through original pores. In addition to the original void volume, the pellets contained at least 20% of the drug. The release properties of the low MW drug from L-PLA and PLA–BSA combination matrix disks are temperature dependent, which may be attributable to both reduction of core solubility in the bulk phase and lowering of leaching of the polymer membrane.

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