The Influence of Thermal Treatment on the Physical-Mechanical and Dissolution Properties of Tablets Containing Poly(DL-Lactic Acid)

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Five molecular weight grades of poly(DL-lactic acid) (PLA) were incorporated as organic and aqueous pseudolatex binders into matrix tablet formulations containing microcrystalline cellulose and the model drug theophylline. The tablets were thermally treated to temperatures above and below the glass transition temperature (T_g) of the PLA. The results of the dissolution studies showed that thermally treating the tablets to temperatures above the T_g of the PLA significantly retarded the matrix drug release compared to tablets which were not thermally treated. The retardation in drug release could be attributed to a stronger compact and a more efficient redistribution of polymer throughout the tablet matrix, based on fundamental principles of annealing. In addition, 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. Gel permeation chromatography and differential scanning calorimetry studies demonstrated that thermal treatment had no significant effect on the molecular weight and the glass transition temperature of (PLA) alone and in combination with other components of the tablet formulation.

KEY WORDS: poly(DL-lactic acid); cellulose; pseudolatex; tablets; thermal treatment; theophylline tablets.

INTRODUCTION

Thermal treatment or annealing of polymers refers to a process by which a polymer is heated to a certain temperature, for a specified time period. Annealing of amorphous polymers usually requires the heating of the polymer to temperatures above the T_g, where the stress relaxation and orientation are the most rapid. After annealing at these high temperatures, the polymer sample is cooled gradually to avoid introduction of unwanted stresses or defects. This type of treatment often influences the mechanical properties of polymers and is associated with the time-dependent nature of the glass transition. In general, annealing increases the density within the polymer compared to quenching processes and decreases the rate of creep or stress relaxation at temperatures below the T_g. These changes tend to improve the dimensional stability of the polymer, as well as remove any residual stresses, strains, or defects that may have occurred during processing. Annealing generally produces polymers which display higher moduli and tend to be more brittle than unannealed polymers (1,2). In reference to the annealing processes just described, the thermal treatment of polymeric pharmaceutical dosage forms has been studied in only a few cases. Curing processes can significantly affect the drug release rate from beads or tablets coated with aqueous polymeric coatings (3–7). In these cases, the curing process can be defined as the heating of the coated product for a specified time period at the end of the coating process. The authors concluded that curing at temperatures above the T_g of the film could significantly improve film formation by ensuring full coalescence of the latex nanoparticles, as well as repairing any strains or defects. This in turn, could reduce the permeability of the film and avoid accelerated and irreproducible dissolution results. In addition, Ghali and coworkers (8) reported on the thermal treatment of pellets containing waxes as matrix retardants. The authors found that heating to temperatures above the melting point of the wax reduced the disintegration of some of the pellet formulations and resulted in a sustained drug release.

In a recent study, we reported on the influence of molecular weight and related properties on the drug release of matrix tablets utilizing PLA as a binder and retardant polymer (9). In the present investigation, the primary objective was to study the influence of thermal treatment on the physical-mechanical and dissolution properties of theophylline tablet formulations containing PLA.

MATERIALS

The five molecular weight grades of poly(DL-lactic acid) (PLA) and other materials used in this study were supplied by various manufacturers: 3500 M_w PLA and microcrystalline cellulose (Avicel PH101), FMC (Princeton, NJ); 42,000 and 138,000 M_w PLA, Birmingham Polymers (Birmingham, AL); 92,000 M_w PLA, Boehringer Ingelheim (Ingelheim, Germany); 553,000 M_w PLA, Dupont (Wilmington, DE); and theophylline anhydrous, Sigma Chemical (St. Louis, MO).

METHODS

Tablet Formulation/Dissolution

The model drug theophylline (25%) was mixed with the excipient (60%) in a twin shell blender. The PLA (15%) was incorporated into the tablet formulation as a binder by dissolving the polymer in methylene chloride to a concentration of 20–30%. A wet granulation process was used to distribute the polymer solution into the powder blend using a conventional bowl mixer. The granulations were then air-dried overnight at room temperature and sieved through a 20-mesh screen. Tablets weighing 300 mg were manually compressed using a Carver 25-ton laboratory press with sufficient force to achieve a solid fraction of 0.72. True density measurements were determined using a helium pycnometer (Micromeritics Corp., Norcross, GA). The solid fraction or porosity was kept constant in order to minimize unwanted variables when comparing drug release and compaction properties.

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Matrix tablets were also prepared using aqueous pseudolatex dispersions of PLA. The pseudolatex was prepared using a process which colloidally dispersed the solid spheres of PLA in water and included a surfactant for stabilization (9–12). The procedure for manufacturing matrix tablets using aqueous dispersions was similar to that using organic solutions of PLA, except for one additional drying step. After air-drying overnight, part of the granulation was heated for 1–2 hr at 60°C. This was done as a curing step to ensure that the polymer within the granulation was fully coalesced without excess water.

A portion of the tablets from all formulations were thermally treated in a conventional oven at 60°C for 24 hr. For one formulation, tablets were also heated to 40 and 80°C. After heating, the tablets were allowed to cool down gradually overnight. Dissolution studies were then performed in 900 mL of water at 37°C using the USP XXII Apparatus 2 at 50 rpm. Samples were analyzed by UV spectroscopy (Beckman) at 270 nm for theophylline. The average dissolution results of three tablets were taken for each granulation. The coefficient of variation was less than ±5% for all results reported (9).

Tableting Indices

The same granulations used to make tablets were used to compress compacts for index testing. Compacts weighing 3 g were compressed to a solid fraction of 0.72 using a Carver press. As with the tablets, a portion of compacts from all formulations was also thermally treated to 60°C for 24 hr and allowed to cool down gradually overnight before indice testing.

Tensile strength testing was achieved using an Instron equipped with a 1-kN load cell. Both sets of compacts, with and without a stress concentrator, were transversely compressed between two platens until a tensile fracture was observed. The speed of the platens was adjusted to maintain a time constant of 10 sec between the maximum force and $1/e$ times that force. The dynamic indentation hardness (P) was determined using a pendulum impact apparatus. The values of the inbound velocity, rebound velocity, and chordal radius were used to calculate the indentation hardness. The indentation hardness serves as an indicator of the shear strength of the compact under a compressive load.

The brittle fracture index (BFI) is defined as BFI = $[T_s/T_{so} - 1]/2$, where T_s is the tensile strength without a stress concentrator and T_{so} is the tensile strength with a stress concentrator. It indicates the ability or inability of a compact to relieve stresses caused by plastic deformation. A BFI value of 0 indicates no brittle behavior, while a BFI of 1 indicates very high brittleness.

The bonding index (BI) is defined as T_s/P and is the ratio of the tensile strength (T_s) of the compact after decompression to the shear strength (P) under a compressive load. It indicates the fraction of strength that survives decompression. It assumes that bonding depends on the true areas of contact formed between particles and that the success of this bonding depends on the areas of true contact that survive decompression, as well as the processes that influence the strength of these contact areas during separation (9,10,13–18).

Molecular Weight Characterization by Gel Permeation Chromatography

The weight-average molecular weight (M_w) was determined using a Waters GPC system with Ultrastyragel columns. Conditions of operation were as follows: solvent, tetrahydrofuran; injection volume, 20 μL; column temperature, 31°C; refractometer temperature, 32°C; flow rate, 1 mL/min; and solute concentration, 0.25% (w/v). The GPC system was calibrated using polystyrene standards in tetrahydrofuran. This allowed the computation of samples of unknown M_w by correlation of the retention time or elution volume with a M_w distribution curve (9,20–22). An average of three determinations was made for each polymer sample.

In order to study the effect of thermal treatment and possible degradation of M_w, virgin polymer samples were placed in small vials and heated for 24 hr at 60°C using a conventional oven. After thermal treatment, the polymer samples were allowed to cool to room temperature, followed by sample preparation and M_w determination as described above. Molecular weight determinations from these thermally treated samples were then compared to those from the nonthermally treated samples. In other degradation studies, 10 300-mg tablets containing 15% (75 mg) of the same grade of PLA were also heated at 60°C for 24 hr. After cooling to room temperature, the tablets were comminuted to smaller particle sizes using a ceramic mortar and pestle. A 167-mg sample of the powder mixture (25 mg PLA) was placed in a vial and brought to volume with 10 mL of tetrahydrofuran. These vials were then sealed and rotated using a Vander-Camp rotator for 2 hr. The vials were then centrifuged, followed by filtering of the supernatant into scintillation vials using a glass syringe. This extraction procedure allowed the indirect measurement of the polymer M_w in the tablet and was repeated with nonthermally treated tablets in order to study the effect of thermal treatment on M_w.

Determination of the Glass Transition Temperature Using Differential Scanning Calorimetry

The glass transition temperatures of PLA were determined using a Perkin Elmer DSC-2C system (Norwalk, CT). Six-milligram samples were heated from 265 to 360 K at 20°C/min and then quenched to 265 K. They were then reheated at the same conditions. The T_g determinations were calculated by extrapolating the linear portion of the thermograms above and below the glass transition and then determining the midpoint. An average of three determinations was made for each polymer sample (9,23,24).

In order to study the influence of thermal treatment, pure polymer samples were placed in a vial and heated to 60°C for 24 hr using a conventional oven. They were then allowed to cool to room temperature overnight and tested the next day. The T_g values of the PLA samples were also evaluated by testing powder samples of tablets containing PLA for both thermally and non-thermally treated tablets. For this case, 15-mg powder samples were weighed and crimped into aluminum pans after comminuting several tablets using a mortar and pestle. These samples were then tested using the same conditions as described for the pure polymer samples.

RESULTS AND DISCUSSION

The data in Fig. 1 show the dissolution profiles of tablets which were thermally treated at different temperatures. The three heating temperatures were chosen relative to the T_g of the pure PLA of 92,000 M_w, which was approximately 53°C. Thermal treatment at 40°C represented heating temperatures below the T_g of the PLA, while thermal treatment at 60 and 80°C represented heating temperatures above the polymer T_g.

Tablets which were pretreated at 40°C showed a small reduction in the drug release as compared to non-thermally treated tablets. However, tablets treated to 60 and 80°C showed much larger reductions in the release of theophylline. The results of this study demonstrated that the effects of thermal treatment were related to the glass transition temperatures of the PLA. Heating the tablets to temperatures above the T_g significantly reduced the rate of drug release compared to tablets which were non-thermally treated, as well as tablets which were heated to temperatures below the the T_g. Physical observation of these tablets during dissolution also demonstrated swelling patterns which supported the differences in drug release. Tablets that were heated to 60 and 80°C exhibited almost no swelling or defects on the matrix surface compared to the other tablets. These results could be attributed to the thermomechanical behavior associated with the T_g. Heating the tablets to temperatures above the T_g of the polymer promoted polymer chain movement, which resulted in a better redistribution of polymer throughout the matrix after cooling. The enhanced distribution strengthened the tablet matrix and resulted in a tablet matrix of higher tortuosity and a lower porosity after swelling. Overall, this process resulted in a reduction in the diffusion and the rate of drug released.

Tablets containing the remaining M_w grades of PLA were also subjected to thermal treatment at 60°C for 24 hr. Dissolution studies were performed and the results are shown in Fig. 2. With the exception of tablets containing the 3500 M_w PLA, thermal treatment had a significant impact on retarding the drug release for each granulation. As seen by the profiles using the Higuchi relationship (25), thermal treatment reduced the rate constant (K) by approximately 20% for each formulation as compared to non-thermally treated tablets. The thermally treated tablets also demonstrated much less swelling than the nontreated tablets. In contrast, thermal treatment had no influence on retarding the drug release for tablets containing the 3500 M_w PLA. Both the thermally and the non-thermally treated tablets disintegrated very quickly, resulting in a rapid drug release. It is important to note that the T_g of the 3500 M_w PLA was below the 37°C dissolution temperature. At that temperature, the modulus of the PLA and the associated strength of the polymer matrix were dramatically lowered regardless of whether the tablets were thermally treated or not (9). In addition, it is important to note that the thermally treated tablets which did not contain any PLA also disintegrated and released theophylline very quickly. This result ruled out any potential retardant effects which could have been brought about by interactions between the other nonpolymeric components of the tablet matrix (10).

Tablet index testing was performed on thermally treated compacts in order to investigate the effect of thermal treatment on the compaction properties of the matrix tablet for-

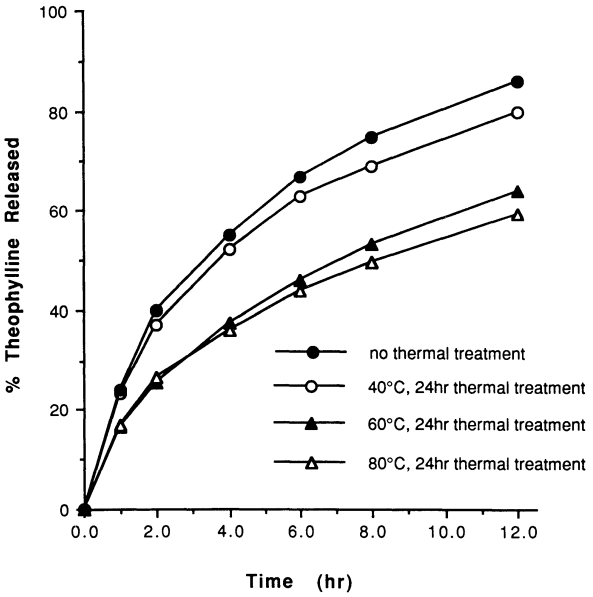

Fig. 1. Influence of thermal treatment temperature on the drug release from tablets containing 15% PLA (92,000 M_w).

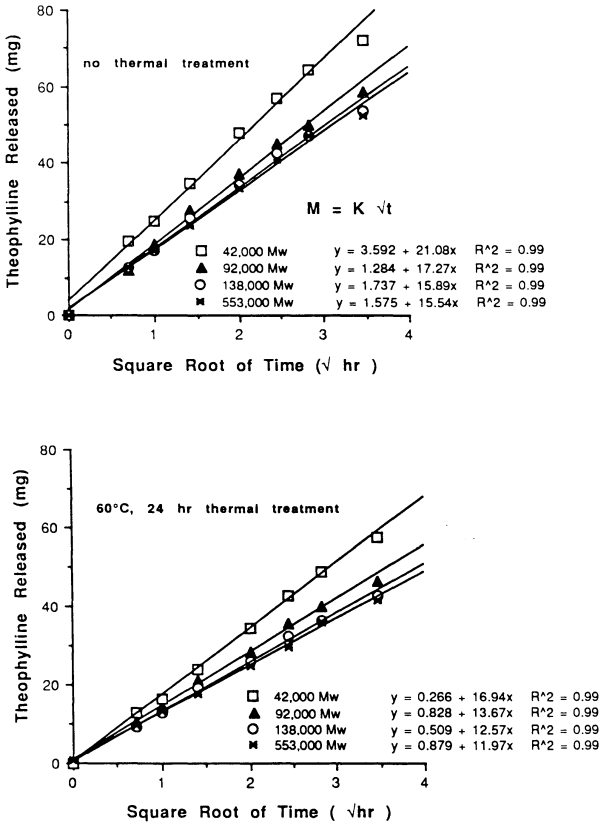

Fig. 2. Effect of thermal treatment and polymer molecular weight on the matrix drug release from tablets containing PLA.

mulations. The results of bonding index testing for both the thermally and the non-thermally treated compacts containing PLA are shown in Table I. With the exception of compacts containing the lowest M_w grade of PLA, thermal treatment significantly increased the bonding index of the compact formulations containing PLA. The compaction results demonstrated a very good correlation with the dissolution profiles of the thermally treated tablets. Thermal treatment, above the T_g of the polymer, resulted in a better distribution of polymer throughout the tablet matrix. After cooling, the enhanced distribution manifested itself in increasing the areas of true contact between the particles of the matrix. This resulted in stronger bonding and a relative reduction in the rate of drug released.

The results of BFI testing for both thermally and non-thermally treated compacts are shown in Table I. Although there appears to be no correlation with M_w, the data indicate that the propensity for brittle behavior generally increased slightly after thermal treatment. However, it is important to note that the brittle fracture index results, on a scale of 0 to 1, were actually very low and indicated an exceedingly small propensity for brittle behavior. Thus, thermal treatment of tablets should not pose any potential problems during processing which may result from minor increases in their brittle propensity.

The compaction properties of tablet formulations containing PLA, as a result of thermal treatment, are also supported by the general effects of annealing on pure polymeric components. As discussed in the Introduction, annealing of polymers often influences the mechanical properties of polymers. In general, annealing decreases the density within the polymer and improves the dimensional stability by raising the modulus (1,2). Slow cooling of annealed polymer also tends to remove any residual stresses, strains, or defects that occurred during processing. Thus, in addition to improving the distribution of polymer and bonding strength within the tablet matrix, 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.

Although thermal treatment improved the bonding capacity within the tablet matrix and retarded the rate of drug release, M_w degradation studies were performed in order to ensure that thermal treatment of the tablet was not degrading the polymer. Gel permeation chromatography studies were conducted on polymer samples that were thermally treated to 60°C for 24 hr, using the same conditions as those used for thermal treatment of tablets. Figure 3 shows that there was a small reduction in M_w after thermal treatment for each M_w grade of PLA. The small reduction in polymer M_w for each PLA sample can be considered to have a minor influence on the mechanical properties of the polymer (9). The relative moduli of the PLA samples are not significantly sensitive to the M_w at temperatures well below their glass transition temperatures. In addition, the thermal stability of PLA is also supported by degradation studies conducted by Gupta and Deshmukh (26).

Degradation studies were also conducted on the 3500 and 92,000 M_w samples of PLA by extracting the polymer from the thermally and non-thermally treated tablets. As illustrated by the bar graphs in Fig. 4, the extracted PLA sample experienced very small M_w reductions after thermal treatment, which were of the same magnitude as that displayed by the pure PLA samples. The results of these degradation studies indicated that processing and manufacturing conditions, as well as the addition of drug and excipient, had no significant effect on lowering the M_w of the PLA. In addition, the results also ruled out the possibility of any excess degradation that could have been caused by thermal treatment and associated interactions between the components of the tablet formulation. Furthermore, these results coincide with the dissolution and compaction data, which demonstrate behavior that is contrary to that which would be expected if there was significant polymer degradation during thermal treatment.

Differential scanning calorimetry (DSC) was conducted on pure PLA samples after thermal treatment in order to investigate possible changes in the T_g that may have occurred. As shown by the transition curves in Fig. 5 for the 3500 and 138,000 M_w PLA samples, the T_g of the polymer samples did not demonstrate any significant changes after thermal treatment. In addition to pure polymer, particulates

Table I. Influence of Thermal Treatment and Molecular Weight on the Bonding Index and Brittle Fracture Index of Compacts Containing Poly (DL-Lactic Acid)

	Bonding index ($\times 10^2$)		Brittle fracture index	
PLA (M_w)	RT[a]	60°C[b]	RT[a]	60°C[b]
3,500	1.85	1.05	0.05	0.01
42,000	2.18	2.95	0.08	0.14
92,000	2.69	3.37	0.06	0.07
138,000	2.87	3.55	0.06	0.08
553,000	2.72	3.25	0.06	0.17

[a] No thermal treatment.
[b] 60°C/24-hr thermal treatment.

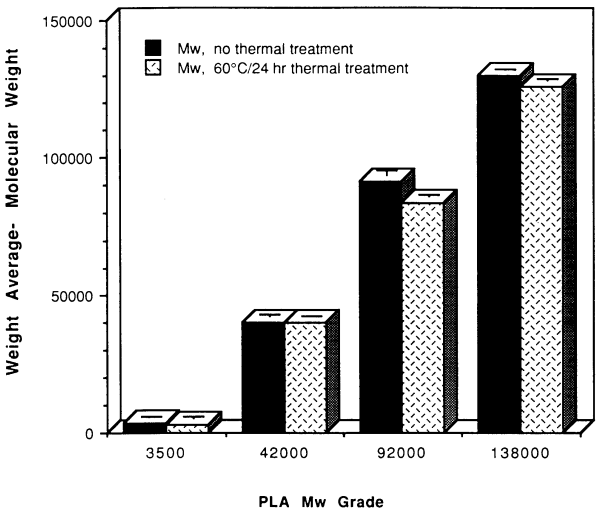

Fig. 3. Effect of thermal treatment on the molecular weight of pure PLA samples.

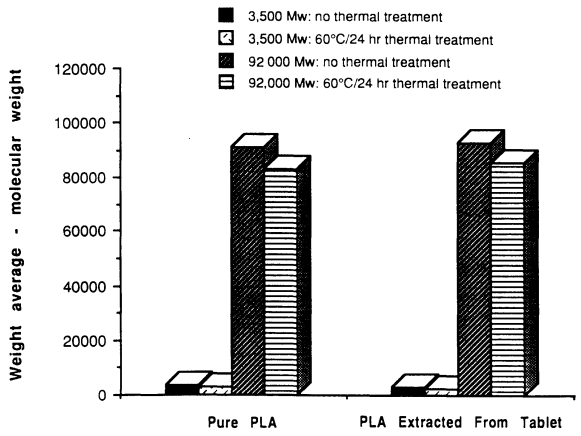

Fig. 4. Influence of thermal treatment on the molecular weight of pure PLA (3500 and 92,000 M_w) and PLA extracted from tablets.

from both thermally and non-thermally treated tablets were also tested using DSC. As seen by the transition midpoints of the tablet samples in Fig. 6, thermal treatment had no effect on the T_g in the tablet samples containing the 138,000 M_w PLA. The results also showed that the T_g of the tablet samples was unchanged compared to the T_g of the pure polymer samples. The DSC analysis was also performed on other tablet samples containing the remaining M_w grades of PLA, with no significant differences in T_g between the samples of pure polymer, as well as those from tablet samples containing PLA. These results indicated that the 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 or by the processing conditions used in tablet manufacturing.

The results in Fig. 7 show the dissolution profiles of tablets containing aqueous dispersions of PLA before and after thermal treatment. In contrast to the method of preparing granulations with organic solutions of PLA, a portion of the granulation utilizing the aqueous dispersions of PLA was dried at 60°C for 1 hr prior to tablet compression. Without any heat drying of the granulation, the drug release from tablets using the aqueous dispersion of PLA was significantly faster than that of the tablets using organic solutions, as well as that of tablets prepared from a granulation that was heat dried. This relative accelerated drug release was supported by the physical observation of the tablets, which showed a substantial amount of swelling and fragmentation of the tablet matrix during dissolution. This effect could be attributed to the residual amount of surfactant in the pseudolatex formulation, which may have enhanced the water penetration and diffusion of drug into the compact. In addition, incomplete coalescence of the polymeric nanoparticles in the pseudolatex could have also resulted in weaker polymer films and an acceleration in the rate of drug release. The drying of the PLA granulation above the T_g of the polymer enhanced the coalescence of the PLA particles, which in turn strengthened the matrix and retarded the drug release. In this case, tablets made from cured granulations demonstrated a drug release profile which was consistent with that of tablets utilizing organic solutions of PLA. During coalescence, the evaporation of the water forced the fusing of individual polymer particles to form a continuous network of polymer in the tablet matrix. This process requires a minimum film-forming temperature above which a continuous film is formed, and which is often the T_g of the polymer (27).

Thermal treatment of tablets prepared from aqueous pseudolatex dispersions of PLA whose granulations were heat-dried showed a reduction in the drug release which was

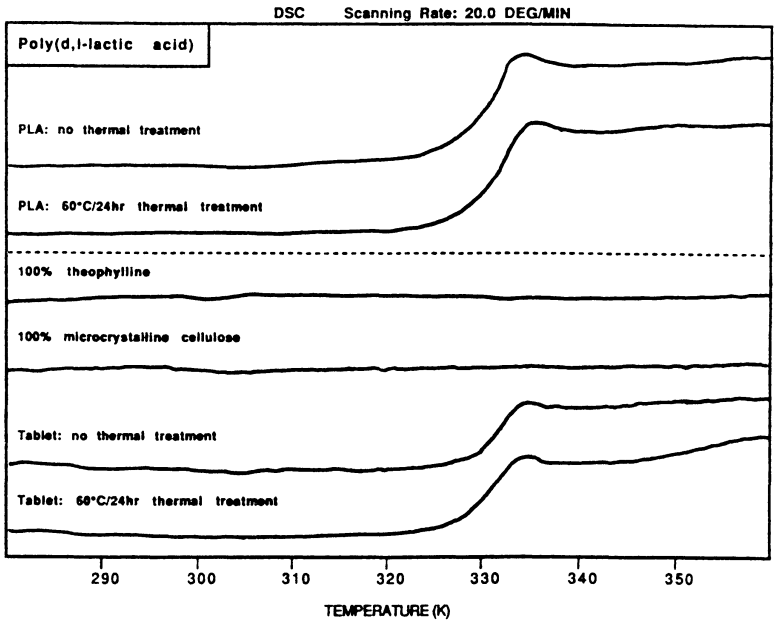

Fig. 5. Influence of thermal treatment on the glass transition temperature of PLA using DSC.

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