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*Research Article*

# The Influence of Polymer Glass Transition Temperature and Molecular Weight on Drug Release from Tablets Containing Poly(DL-lactic Acid)

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Five molecular weight grades of poly(DL-lactic acid) were characterized using gel permeation chromatography, differential scanning calorimetry, and viscometry to determine the effect of molecular weight on the glass transition temperature and the intrinsic viscosity. In addition, dynamic mechanical thermal analysis was used to assess the dynamic storage modulus and the damping factor of the polymer samples by detecting motional and structural transitions over a wide temperature range. Significant relationships were found between the molecular weight and these polymer properties. The five grades of poly(DL-lactic acid) were also incorporated as binders into matrix tablet formulations containing the model drug theophylline and microcrystalline cellulose. Dissolution studies showed significant correlations between the properties of the polymer and the matrix release profiles of the tablets. The release of theophylline slowed down progressively as the polymer molecular weight increased. The differences in release became less significant and reached a limiting asymptotic value as the molecular weight increased to 138,000. Further, tablet index testing was utilized to determine the compaction properties of the polymer granulations. Although there was no correlation with the molecular weight of PLA, brittle fracture index testing indicated very low brittleness for all granulations tested. However, bonding index determinations correlated very well with both the physical-mechanical properties of the polymer and drug release profiles.

**KEY WORDS:** poly(DL-lactic acid); glass transition temperature; molecular weight; dynamic mechanical thermal analysis; matrix tablets; tableting indices.

## INTRODUCTION

Poly(DL-lactic acid) (PLA) is an amorphous, water-insoluble, aliphatic polyester polymer which has found wide utility for many applications in medicine. Important properties include its nontoxicity, sterilizability, and miscibility with other polymers and adjuvants. It has been classified as a biocompatible and biodegradable polymer. *In vivo,* it eventually undergoes slow hydrolytic deesterification to lactic acid, a normal metabolite in the glycolytic cycle of carbohydrate metabolism (1–4).

PLA can be synthetically polymerized in a wide range of molecular weights by two processes. The first process utilizes a direct condensation reaction in which the lactic acid monomer is polyesterified to low molecular weight forms of PLA (5). The second and more popular process is used to produce higher molecular weight grades of PLA. It first utilizes the conversion of lactic acid to the lactide cyclic dimer (dilactide), with subsequent ring-opening polymerization using high heat and catalysts (6). The molecular weight is an important polymer property because it can greatly affect other chemical and physical-mechanical properties such as the solubility, viscosity, diffusivity, modulus, and glass transition temperature.

Because of its biodegradability, PLA was first investigated for use in surgical repair materials, as well as systems for implantation and insertion such as nonremovable sutures and bone plates (1,7). Current pharmaceutical investigations using PLA have focused on potential applications for controlled-release implantation systems, microspheres, microcapsules, and sustained-release coating formulations (8–12). In the present investigation, the primary objective was to study the influence of molecular weight and related properties on the drug release from matrix tablets containing PLA.

## MATERIALS

Various molecular weight grades of PLA were supplied from different manufacturers: the 3500 weight-average molecular weight ($M_w$) was kindly supplied by FMC (Princeton, NJ), and the 42,000 and 92,000 $M_w$ PLA samples were obtained from Birmingham Polymers (Birmingham, AL). The 138,000 $M_w$ polymer was supplied by Boehringer Ingelheim (Ingelheim, Germany) and the 553,000 $M_w$ polymer was purchased from Dupont (Wilmington, DE). Theophylline anhydrous was obtained from Sigma Chemicals (St. Louis,

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MO). Microcrystalline cellulose (Avicel, PH101) was donated by FMC Corp. (Princeton, NJ).

## METHODS

### Molecular Weight Characterization by Gel Permeation Chromatography (GPC)

Molecular weight determinations were made using a Waters GPC system with Ultrastyragel columns having exclusions limits of $10^4$, $10^3$, and $10^2$ Å. Other 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 unknown molecular weights samples by correlating the retention time or volume with a molecular weight distribution curve. Both the weight-average ($M_w$) and the number-average ($M_n$) molecular weights were calculated from the following equations:

$$M_w = (\Sigma N_x M_x^2)/(\Sigma N_x M_x) \quad \text{and} \quad M_n = (\Sigma M_x N_x)/(\Sigma N_x) \tag{1}$$

where $N_x$ is the number of polymer molecules of each molecular weight species $M_x$. The polydispersity was calculated by dividing the weight-average molecular weight by the number-average molecular weight (13–15). An average of three determinations was made for each polymer sample.

### Differential Scanning Calorimetry (DSC)

The PLA glass transition temperatures were determined using a Perkin Elmer DSC-2 system interfaced with a thermal analysis data station computer (TADS). Six-milligram samples were weighed and crimped into aluminum pans. Samples were heated from 265 to 355 K at 20°C/min and then quenched to 265 K. They were then reheated under 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. The system was calibrated using an indium standard (16). An average of three determinations was made for each polymer sample.

### Viscosity

Viscosity measurements were made using dilute-solution viscometry at 25°C. An Ostwald-Fenske capillary viscometer (Model 25-1332) was used to determine the relative and inherent viscosities of dilute PLA solutions in methylene chloride. A minimum of four concentrations was used. The equation for inherent viscosity is

$$\eta_{inh} = (\ln \eta_r)/C \tag{2}$$

The relative viscosity, $\eta_r = t/t_o$, is the ratio of the flow time of the polymer solution to the flow time of the solvent; $C$ is the concentration of the polymer solution. A mean of three readings was used to determine the inherent viscosity at each concentration for each PLA sample. The intrinsic viscosity [η] was determined by extrapolation to zero concentration from the linear plots of the inherent viscosity-versus-concentration data (14,15).

$$[\eta] = [(\ln \eta_r)/C]_{c=o} \tag{3}$$

### Dynamic Mechanical Thermal Analysis (DMTA)

Dynamic mechanical thermal analysis of polymers is an extremely useful technique for studying glass transitions, secondary transitions, and storage moduli over a wide temperature and frequency range. It is especially sensitive to the chemical and physical morphology of polymers and is considered the most sensitive test for detecting all motional and structural transitions (17). DMTA measures the response of a polymer to a forced oscillation which may be of sinusoidal or other periodic forms. Because the stress and strain are not in phase, dynamic mechanical thermal analysis can determine the dynamic storage modulus and damping factor of a polymer. Variations of the dynamic storage modulus and damping factor with temperature and frequency allow the characterization of the viscoelastic properties of polymers. Young's modulus ($E'$) is the initial slope of the stress/strain curve and reflects the stiffness and strength of the polymer. It is one of the most basic and structurally important of all of the mechanical properties. The damping factor or loss tangent, denoted Tan $\partial$, measures the ratio of energy dissipated as heat to the maximum energy stored in the polymer for one cycle of oscillation. It is a measure of the imperfection in elasticity of a material. It is used to detect secondary transitions, as well as the glass transition temperature, which is reflected as a maximal peak in the curve of the damping factor versus temperature (14,17–19).

Molded polymer samples, with dimensions of 12.5 × 8.0 × 3.1 mm, were prepared using a Wabash compression molding apparatus. The samples were compression molded at temperatures slightly above the $T_g$ of each polymer used. The samples were automatically cooled to room temperature by a jacketed cooling unit on the press and then removed for testing. The polymer samples were clamped in the DMTA apparatus (Polymer Labs, Shropshire, UK) and then covered with a cyrogenic cooling/heating unit. An oscillation frequency of 3 Hz and a strain or displacement of 63 μm was forced on the polymer while the temperature increased from −100 to 75°C at a rate of 2°C/min. The DMTA was interfaced with a computer which calculated and plotted Young's modulus and Tan $\partial$ versus the selected temperature range for each polymer sample.

### Tablet Formulations/Dissolution

The model drug theophylline (25%) was mixed with microcrystalline cellulose (60%) in a twin-shell blender. The PLA (15%) was incorporated into the tablet formulations as a binder solution by dissolving the polymer in methylene chloride to a concentration of 20–30%. A wet granulation process was then used to distribute the polymer solution into the powder blend using a conventional bowl mixer. Matrix tablets were also prepared by incorporating the polymer into the powder blend as an aqueous pseudolatex dispersion. The pseudolatex was prepared using a process which colloidally dispersed the solid spheres of PLA in water and included a

surfactant for stabilization. For both the organic and the aqueous systems, the granulations were air-dried overnight at 25°C and passed through a 20-mesh screen. Tablets weighing 300 mg were compressed using an instrumented Carver press. The tablets were compressed using a sufficient force to achieve a solid fraction of 0.72; solid fraction = [1 − porosity]. The solid fraction is the ratio of the apparent density over the true density of the tablet. The true density was determined using a helium pycnometer (Micromeritics Instrument Corp., Norcross, GA).

Dissolution studies were performed in 900 ml of water at 37°C using the USP XXII, Apparatus 2. The paddle speed was maintained at 50 rpm. Samples of the dissolution media were taken over a period of 12 hr and analyzed by UV spectroscopy (Beckman DU) at a maximum wavelength of 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.

### Tableting Indices

The same granulations used to make tablets were used to compress compacts for tablet index testing. Compacts weighing 3 g were compressed to a solid fraction of 0.72 using a Carver press modified with a load cell. The compacts were compressed using a 0.75-in.$^2$ die with two square flat-faced punches. The die was split along a line through one diagonal and was capable of triaxial decompression. One set of compacts was compressed with a 1-mm axially oriented hole. This served as a stress concentrator for tensile testing. Compacts were made for each granulation containing the five molecular weight grades of PLA. An average of four compacts was used for each of the following determinations.

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 maximum force required to produce the tensile fracture was recorded as the tensile strength.

Dynamic indentation hardness (P) was determined using a pendulum impact apparatus. The compacts were held in a die with one side exposed to the path of the sphere of the pendulum. A ballistic sensor measured the inbound and rebound velocity of the sphere. The chordal radius of the resulting dent in the compact was measured under the low-power objective of a microscope. 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

$$\mathrm{BFI} = [Ts/Ts_o - 1]/2 \quad (4)$$

where $Ts$ is the tensile strength without a stress concentrator and $Ts_o$ 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 high brittleness.

The bonding index (BI) is defined as $T_s/P$: the ratio of the tensile strength of the compact after decompression to the shear strength 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 (20–24).

## RESULTS AND DISCUSSION

The data in Table I show the comparisons of molecular weights, molecular weight distributions, intrinsic viscosities, and glass transition temperatures of five different PLA samples used in the tablet and compact formulations. The profile in Fig. 1 shows the relationship of molecular weight to the intrinsic viscosity. As expected, the increase in viscosity is proportional to the weight-average molecular weight ($M_w$) as given by the Mark-Houwink equation:

$$[\eta] = K M_w^a \quad (5)$$

where $a = 0.66$ and $K = 3.3 \times 10^{-4}$. The $K$ and $a$ are constants for a given polymer type, solvent, and temperature. This correlation curve can be used to predict empirically the molecular weight of unknown samples of PLA (14,15,25).

The glass transition temperature increased from 27°C for the lowest molecular weight PLA (3,500) to 57°C for the highest molecular weight PLA (553,000). However, the differences in $T_g$ became progressively less significant as the molecular weight increased from 92,000 to 553,000, reaching a plateau at 57–58°C, as shown in Fig. 2. This was expected, since the glass transition is dependent on the free volume of the polymer. At the glass transition, the energy supplied is sufficient enough to move large segments of polymer chains (20–50 consecutive carbon atoms). This motion requires additional free volume and is associated with a significant change in the expansion coefficient of the polymer. Macroscopically, the rigid glassy state of an amorphous polymer becomes a viscous liquid or rubber producing drastic changes in the physical-mechanical properties of the polymer. The change in $T_g$ arises from the fact that as the polymer molecular weight increases, there are fewer chains ends which have less free volume than the same number of atoms in the middle of the chain. The decrease in free volume gradually reaches a limit as the molecular weight increases because of chain entanglements. In the same manner, the energy required to produce the excess free volume, as reflected

Table I. Chemical and Physical-Mechanical Properties of Five Grades of Poly(DL-lactic Acid)

| Sample | $M_w$ | $M_n$ | $M_w/M_n$ | $[\eta]$ | $T_g$ (°C) |
|---|---|---|---|---|---|
| 1 | 3,450 | 1,473 | 2.34 | 0.08 | 27 |
| 2 | 41,715 | 24,148 | 1.73 | 0.33 | 44 |
| 3 | 92,360 | 46,032 | 2.20 | 0.71 | 53 |
| 4 | 137,619 | 71,253 | 1.93 | 0.94 | 56 |
| 5 | 552,846 | 262,697 | 2.10 | 2.00 | 57 |

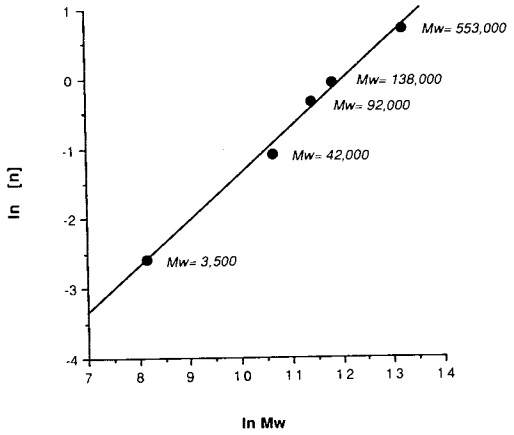


Fig. 1. Intrinsic viscosity–weight-average molecular weight relationship for PLA in methylene chloride at 25°C.

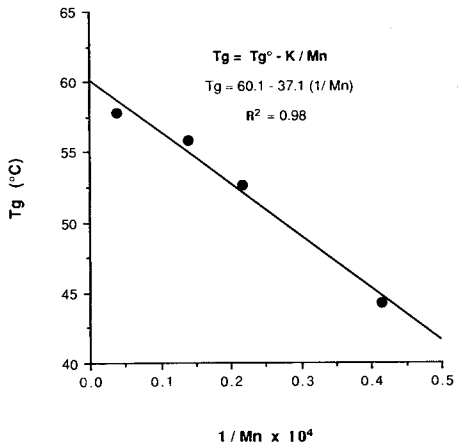


Fig. 3. Relationship between the glass transition temperature and the reciprocal of the number-average molecular weight for PLA.

by the $T_g$, also reaches a limiting value. This relationship is given by the following equation:

$$T_g = T_g^\circ - K/M_n \quad (6)$$

where $T_g^\circ$ is the limiting $T_g$ of a material of infinite molecular weight, $M_n$ is the number-average molecular weight, and $K$ is a constant characteristic of every polymer (17,18,26,27). The data in Fig. 3 show that the $T_g$ of PLA follows this relationship in the practical range of molecular weights, with a $T_g^\circ$ of 60°C.

In Fig. 4, dynamic mechanical thermal analysis demonstrates the relationship between the damping factor and Young's modulus ($E'$) over a wide temperature range for the 92,000 $M_w$ sample of PLA. As anticipated, the modulus is relatively constant until it reaches the region of the glass transition. In this region, the modulus–temperature curve goes through an inflection point in which the modulus falls dramatically, approximately three decades. This can be interpreted macroscopically as a change from a stiff and rigid polymer to the onset of liquidlike or rubbery motion. This phenomenon is also reflected by the damping factor (Tan ∂) or loss tangent curve, which peaks to a maximum at the glass transition temperature. The damping factor is associated with small chain segment movement caused by partial loosening of the polymer structure. Because the glass transition temperature is not a true constant, but a function of the time scale of the experiment, caution should be taken when comparing the glass transition temperature obtained from dynamic experimentation to other methods (18). Although the glass transition temperatures determined from DMTA correlate very well with those from DSC, the peak of the Tan ∂ curve at a frequency of 1 cycle per sec is generally 5 to 10°C above the glass transition temperature as determined from DSC experimentation.

As mentioned previously, the mechanical properties of polymers are very dependent on the glass transition temperature. In fact, the glass transition temperature is the most important characteristic as far as mechanical properties are concerned. With the exception of low molecular weight grades, the polymer modulus is nearly independent of molecular weight at temperatures well below the glass transition region. However, at temperatures near and above the $T_g$, the modulus has a much larger dependence on molecular weight. The results in Fig. 5 show the influence of temperature and molecular weight on the Young's modulus of PLA. At each testing temperature, the modulus increased with molecular weight up to a maximal value which was dependent on the position of the testing temperature relative to the glass tran-

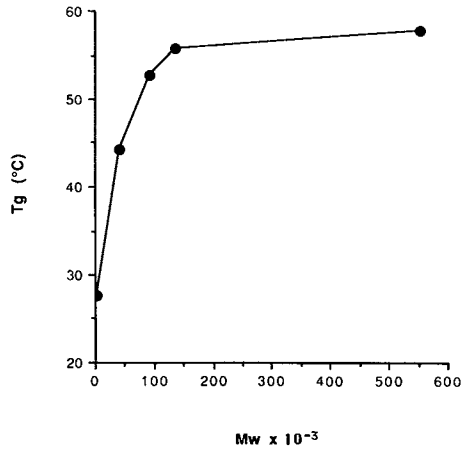


Fig. 2. Influence of molecular weight ($M_w$) on the glass transition temperature ($T_g$) of PLA.

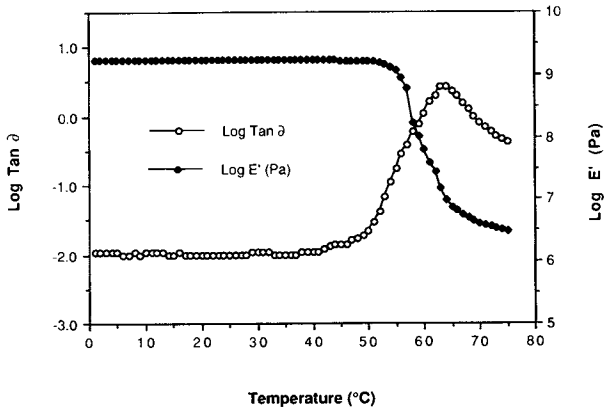


Fig. 4. Influence of temperature on Young's modulus ($E'$; pascals) and the damping factor (Tan ∂) for PLA ($M_w$ = 138,000).

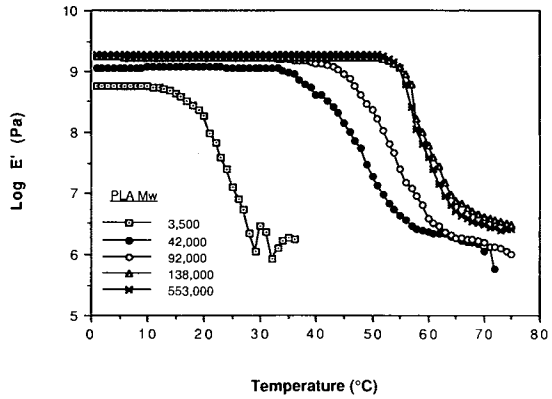


Fig. 5. Influence of temperature and molecular weight on the Young's modulus ($E'$) of PLA using dynamic mechanical thermal analysis (DMTA).

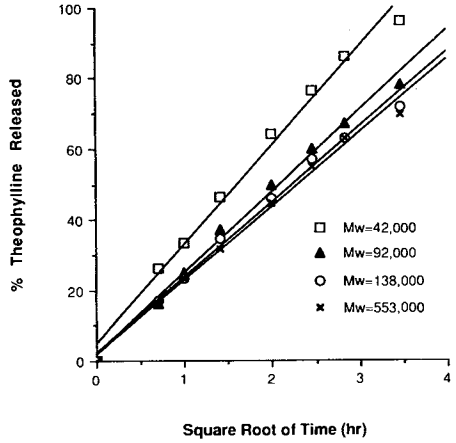


Fig. 7. Influence of molecular weight on the matrix drug release from tablets containing PLA.

sition temperature. At 25°C, there were minor differences between the log moduli of the 42,000 through 553,000 $M_w$ samples. However, the 3500 $M_w$ sample did show a substantial decrease in the log modulus. It is important to note that the 3500 $M_w$ sample was near its glass transition at 25°C, resulting in approximately a three-decade decrease in its modulus. As the temperature increased toward the glass transitions of the remaining polymers, the differences between the moduli of the polymer samples became more pronounced.

The results of the dissolution trials for tablets containing the different molecular weight samples of PLA are shown in Fig. 6. The release of theophylline slowed down progressively as the molecular weight increased from 3500 to 553,000 $M_w$. However, as with the other polymer properties, the differences in sustaining drug release became less significant and reached a maximum for tablets containing PLA of 138,000 $M_w$. With the exception of the 3500 $M_w$ sample, all tablets containing the higher molecular weight polymers demonstrated a matrix drug release mechanism. This was evidenced by the results of the dissolution profiles plotted using the well-known linear Higuchi matrix release relationship that occurs when the percentage released is plotted versus the square root of time, as shown in Fig. 7 (28). Physical observations also supported matrix drug release. The initial swelling of the tablets decreased as the molecular weight of the polymer increased. The observed swelling was a function of the insoluble microcrystalline cellulose in the formulation, which at 60%, acted as a wicking and swelling agent prone to causing disintegration in conventional tablet formulations (29). Following tablet swelling, release was primarily controlled by a diffusion pathway through the polymer–excipient matrix. In support of this proposed drug release mechanism, the SEM photograph in Fig. 8 displays the surface morphology of the tablet matrix after 12 hr of dissolution. It can be seen that the polymer is acting as a web or network which holds the excipient together and prevents the disintegration of the matrix. The only exceptions to this observation occurred with the tablets containing the 3500 $M_w$ PLA, which rapidly disintegrated and released 100% drug within the first hour.

The profiles in Fig. 9 show the relationship of the polymer modulus and the amount of drug released after 6 hr of dissolution at 37°C, to the molecular weight of the polymer. The increase in the modulus at 37°C was inversely proportional to the amount of drug released from the tablet matrix. It is important to note that as the polymer modulus reached an asymptotic value with molecular weight, the tablet drug release also reached a limiting value at the same polymer molecular weight of 138,000. This relationship demonstrates

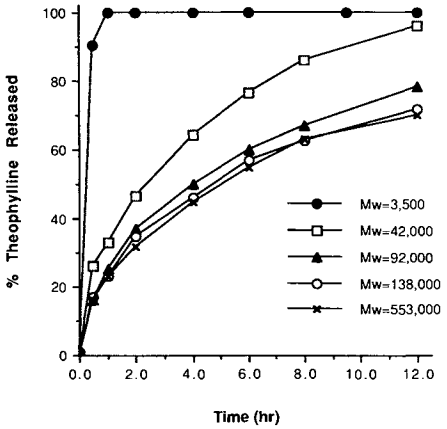


Fig. 6. Influence of molecular weight on the drug release from tablets containing PLA.

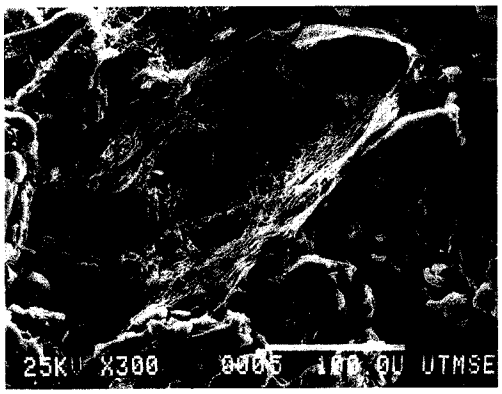


Fig. 8. Scanning electron micrograph of tablet surface following 12-hr dissolution test.

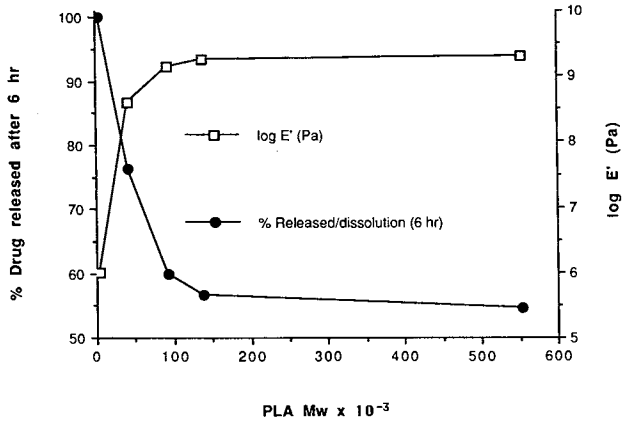


Fig. 9. Effect of molecular weight on the polymer modulus ($E'$) and the percentage of drug released after 6 hr of dissolution at 37°C from tablets containing PLA.

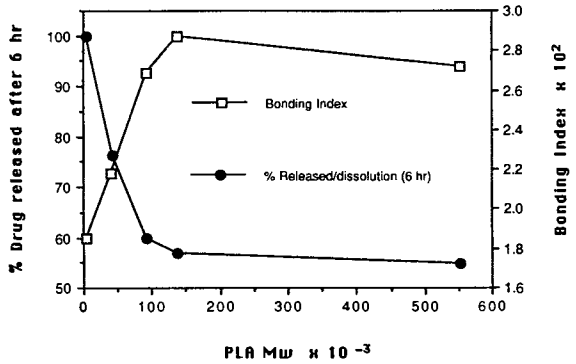


Fig. 10. Effect of molecular weight on the bonding index and the percentage of drug released after 6 hr of dissolution at 37°C from tablets containing PLA.

the importance of molecular weight on the physical-mechanical properties of the polymer, such as the modulus, and its effect on drug release. In addition, the data indirectly demonstrate the dependence of the polymer modulus on the temperature of the dissolution media relative to the glass transition temperature. The dissolution temperature (37°C) was well above the glass transition temperature of the 3500 $M_w$ PLA contained within the tablet matrix. At that temperature, the modulus of the PLA was dramatically lowered, allowing the disintegrating properties of the microcrystalline cellulose to overcome the binding and matrix effects of the polymer.

The results of the tablet index testing for bonding index (BI) and brittle fracture index (BFI) are reported in Table II. Although there was no correlation between the brittle fracture index and the molecular weight of polymer used, the formulations demonstrated very low brittleness, as reflected by a BFI of 0.05–0.08 on a scale of zero to one. However, bonding index testing provided interesting results which correlated very well with the physical-mechanical properties of the polymer, as well as the drug release during dissolution. Similar to the polymer modulus, increasing bonding indices correlated well with increasing molecular weight of the PLA, while being inversely related to the rate of drug release during dissolution. This bonding success is reflective of the survival of bond strength during the decompression process which is formed by areas of true contact (20–24). The results in Fig. 10 show that the bonding index reached a maximum value of $2.87 \times 10^{-2}$. At the same time, the amount of drug released reached a minimum for tablets containing PLA of 138,000 molecular weight. These results demonstrate that increasing polymer molecular weight promoted higher levels of bonding between granules of the formulation. Increased bonding manifested itself in lowering the diffusion of drug from the tablet matrix, as reflected by a lower drug release rate. These results also indicate that there is a limit to the influence of polymer molecular weight on bonding and the amount of drug released.

Table II. Influence of Polymer Molecular Weight on the Bonding Index and Brittle Fracture Index of Compacts Containing Poly(DL-lactic Acid)

| PLA ($M_w$) | Bonding index ($\times 10^2$) | Brittle fracture index |
|---|---|---|
| 3,500 | 1.85 | 0.05 |
| 42,000 | 2.18 | 0.08 |
| 92,000 | 2.69 | 0.06 |
| 138,000 | 2.87 | 0.06 |
| 553,000 | 2.72 | 0.06 |

The results presented thus far were prepared from tablets utilizing organic granulating solutions of PLA which provided meaningful conclusions concerning the mechanisms of drug release and compaction properties. Present studies are focusing on the use of aqueous pseudolatex dispersions of PLA for well-known safety and environmental reasons (12,30). The dissolution results of tablets formulated with an aqueous pseudolatex dispersion of the 92,000 molecular weight PLA are shown in Fig. 11. The drug release was significantly faster than that from tablets granulated with the organic solvent. This was possibly due to a small but significant amount of surfactant in the latex formulation, as well as incomplete coalescence of the polymeric nanoparticles in the pseudolatex dispersion. A thermal treatment process was developed in which the tablets were preheated to tem-

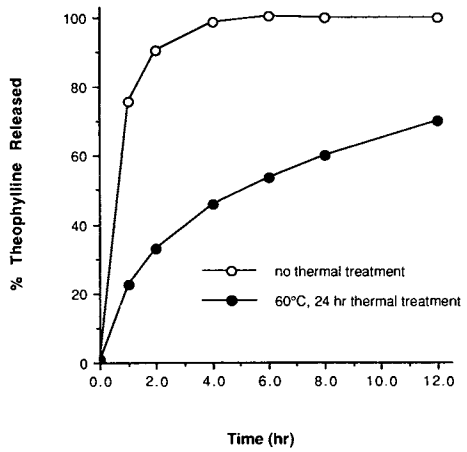


Fig. 11. Influence of thermal treatment on the drug release from tablets granulated with an aqueous pseudolatex dispersion of PLA ($M_w$ = 92,000).

peratures above the glass transition temperature of the PLA in the tablet matrix. The dissolution results demonstrate that the drug release rate was significantly retarded and comparable to the release of tablets prepared from organic solutions of PLA. Future studies will address the use of aqueous pseudolatexes of PLA as potential binding agents in tablet formulations for controlled release, as well as the effects of thermal treatment.

In conclusion, the chemical and physical-mechanical properties of PLA such as the molecular weight, glass transition temperature, and dynamic modulus greatly influence the compaction and drug release properties of tablets containing poly(DL-lactic acid). The principles discussed concerning the relationships between these chemical and physical-mechanical properties are universal to most polymers and can be used to study other controlled-release polymeric systems.

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