ELSEVIER

Journal of Controlled Release 70 (2001) 71–82

journal of controlled release

www.elsevier.com/locate/jconrel

# Effect of molecular weight and glass transition on relaxation and release behaviour of poly(DL-lactic acid) tablets

R. Steendam[a,*], M.J. van Steenbergen[b], W.E. Hennink[b], H.W. Frijlink[a], C.F. Lerk[a]

[a]*Department of Pharmaceutical Technology and Biopharmacy, Groningen University Institute for Drug Exploration, University of Groningen, Ant. Deusinglaan 1, 9713 AV Groningen, The Netherlands*

[b]*Department of Pharmaceutics, Faculty of Pharmacy, Utrecht University, PO Box 80.082, 3508 TB Utrecht, The Netherlands*

Received 27 March 2000; accepted 5 September 2000

**Abstract**

Different molecular weight grades of poly(DL-lactic acid) were applied as release controlling excipients in tablets for oral drug administration. The role of molecular weight and glass transition in the mechanism of water-induced volume expansion and drug release of PDLA tablets was investigated. Modulated differential scanning calorimetry (MDSC) was used to determine the glass transition temperature of both dry and hydrated PDLA samples. The absorption rate and total amounts of sorbed water by the polymer were determined by dynamic vapour sorption (DVS). Expansion behaviour of PDLA tablets was measured using thermal mechanical analysis (TMA). At 95% relative humidity all molecular weight grades of PDLA sorbed 1.1–1.3% w/w water, as was determined with DVS. MDSC showed glass transition temperature reductions of 10–11°C for all molecular weight grades of PDLA in water. Volume expansion studies using TMA showed that the molecular relaxation time and equilibrium porosity of the tablets increased with molecular weight. The mean relaxation time increased exponentially with the temperature interval $T_g - T$. The onset temperature of shape recovery of hydrated tablets was approximately 8°C lower than for dry samples. Drug release was only slightly affected by molecular weight. It is concluded that volume expansion of compressed PDLA tablets is related to the glass transition behaviour, originates from water-induced and thermally stimulated shape memory behaviour and is therefore highly dependent on the molecular weight of PDLA. 

*Keywords:* Poly(DL-lactic acid) tablets; Plasticisation; Glass transition temperature; Thermal mechanical analysis; Molecular relaxation time; Shape memory

## 1. Introduction

Poly(DL-lactic acid) (PDLA) is well known for its highly biocompatible and biodegradable character and has been widely investigated for application in medical and pharmaceutical devices [1,2]. Current pharmaceutical investigations using PDLA have

*Corresponding author. Present address: Polyganics BV, L.J. Zielstraweg 1, 9713 GX Groningen, The Netherlands. Tel.: +31-50-588 6583; fax: +31-50-588 6599.

*E-mail address:* mail@polyganics.com (R. Steendam).

0168-3659/01/$ – see front matter 
PII: S0168-3659(00)00342-4

focused on potential applications for implantable sustained release systems [3], microspheres [4] and microcapsules [5]. During the last decade, an increasing number of papers [6–11] and patents [12,13] reported the application of PDLA as a sustained release excipient in tablets. Previously we reported on the suitability of PDLA as a release controlling polymer in tablets prepared by direct compression [14].

PDLA is a hydrophobic, amorphous polymer, which can sorb small amounts of water, but does not dissolve or swell in an aqueous environment. However, these small amounts of water have been found to have a marked plasticising effect resulting in a significant reduction of the glass transition temperature of the polymer [15–17]. Previously, we discussed the reduction of the glass transition temperature of PDLA in the presence of water and the consequences thereof for water uptake and drug release characteristics of PDLA tablets, which had been prepared by direct compression at temperatures below the glass transition of PDLA [18,19]. It was found that the water-induced reduction of the glass transition of PDLA by 10–15°C resulted in entropy-driven relaxation of plastically deformed PDLA at temperatures around the glass transition of the hydrated polymer (shape memory behaviour). This shape memory behaviour resulted in shape recovery of deformed powder particles and volume expansion (and consequently porosity increase) of the tablets as a whole. This novel water-induced and thermally stimulated mechanism has been thoroughly investigated and discussed previously [18,19]. From expansion studies at different temperatures, it was concluded that the rate of water uptake, which is the first and most important step in the overall release mechanism, was determined by the relaxation rate of the polymer.

Relaxational behaviour of polymers is highly dependent on the molecular weight and glass transition temperature. In order to investigate the suitability of PDLA as a release controlling excipient in tablets, a thorough understanding of the effect of molecular weight and glass transition temperature on water uptake and drug release is required. Therefore, the primary objective of this study is to investigate plasticisation of various molecular weight grades of PDLA and the effect of molecular weight and glass transition temperature on relaxational behaviour of the polymers. The consequences for volume expansion behaviour of the tablets and drug release will be discussed.

## 2. Materials and methods

### 2.1. Materials

Biomedical grade poly(DL-lactic acid) polymers (PDLA) containing 50% D-lactide and 50% L-lactide with viscosity averaged molecular weights ($M_v$) of $12.5\times10^3$, $21.7\times10^3$, $41.8\times10^3$, $69\times10^3$, $136.5\times10^3$ and $241.5\times10^3$ and with residual monomer contents <1% were supplied by PURAC Biochem (Gorinchem, The Netherlands). $M_v$ $85\times10^3$ PDLA, containing 25% D-lactide and 75% L-lactide and a residual monomer content of 4.5% [14,18] was supplied by Hycail (Noordhorn, The Netherlands) (Table 1). Viscosity-average molecular weights ($M_v$) were calculated from the intrinsic viscosity (chloroform, 25°C, Ubbelohde viscosimeter) using Mark-Houwink constants $K=2.21\times10^{-4}$ and $a=0.77$. Theophylline monohydrate (Genfarma, Maarsen, The Netherlands) was used as a model drug. The granules were cooled by adding solid carbon dioxide and subsequently milled in a Pulverisette®14 mill (Fritsch, Idar-Oberstein, Germany). The sieve fraction <180 μm was collected. The true densities of

Table 1
Chemical and physical–mechanical properties of poly(DL-lactic acid) polymers[a]

| $[\eta]$ [dl/g] | $\rho$ [g/cm$^3$] | $M_v$ | $T_g$ [°C] | $M_w/M_n$ |
|---|---|---|---|---|
| 0.31[b] | 1.2467 | 12500 | 35.7 | 1.90 |
| 0.48[b] | 1.2440 | 21700 | 45.8 | 2.57 |
| 0.80[b] | 1.2541 | 41800 | 47.8 | 2.80 |
| 1.17[b] | 1.2535 | 69000 | 49.0 | 6.34 |
| 1.99[b] | 1.2550 | 136500 | 49.5 | 3.11 |
| 3.08[b] | 1.2585 | 241500 | 50.2 | 4.37 |
| 1.44[c] | 1.2437 | 85000 | 48.6 | N.D. |

[a] $[\eta]$, intrinsic viscosity; $\rho$, density; $M_v$, viscosity average molecular weight; $T_g$, glass transition temperature of dry polymer; $M_w/M_n$ represents the polydispersity of the samples as determined by gel permeation chromatography.
[b] Supplied by Purac Biochem.
[c] Supplied by Hycail.

theophylline monohydrate (1.460 g/cm$^3$) and PDLA (Table 1) were measured at 22°C by a helium pycnometer MVP-1 (Quantachrome Corp., Syosset, NY, USA).

### 2.2. Methods

For gel permeation chromatography the samples were dissolved in chloroform (HPLC grade, Biosolve, Valkensward, The Netherlands) to a final concentration of 1 mg/ml and filtered (Polypure filter, 13 mm, 0.45 μm, Alltech, Deerfield, USA). The system consists of a Waters 510 HPLC pump, a Waters 410 differential refractometer (Waters Associates Inc., Milford, USA) with three thermostated (35°C) columns (Sodex KF-series, KF-80P 4×10 mm, precolumn; KF-80M, 8×250 mm, exclusion limit 2E7 Da; KF-801, 8×250 mm, exclusion limit 1500 Da; Showa Denko, Tokyo, Japan). Chromatograms were analysed with Millennium 3.0 software (Waters Associates Inc, Milford, USA) with tge GPC option installed. Molecular weights are relative to Polystyrene standards.

Physical mixtures of PDLA and theophylline monohydrate (20% w/w) were prepared by mixing the compounds in a Turbula mixer (Bachoven, Basle, Switzerland) at 90 rpm for 30 min. No additional compounds were added. Cylindrical flat-faced PDLA compacts (200 mg, diameter 9 mm) containing 40 mg drug were prepared on a hydraulic press (ESH Testing, Brierley Hill, UK) at 157 MPa and a load rate of 7.5 MPa/s. The maximum compaction pressure was held for 0.1 s. Porosities of the tablets were calculated from the weight and dimensions of the tablets and the true densities of the powders.

Thermal analyses were conducted under nitrogen using a Modulated DSC 2920 (TA Instruments, New Castle, DE, USA) and an indium standard. Prior to analysis, hydrated tablets were grounded and surface water was removed with a tissue. Samples (10–15 mg) were cooled to −20°C before heating to 80°C at a background heating rate of 2°C/min with a ±1°C amplitude over a 60 s period. $T_g$s were calculated by extrapolating the linear portion of the thermograms of the reversible heat flow above and below the glass transition, respectively, followed by determination of the midpoint.

Sorption behaviour of the powders was analysed at 25°C and a relative humidity of 95% using a dynamic vapour sorption DVS-1000 instrument (Surface Measurement Systems Ltd., London, UK) instrumented with a Cahn D200 microbalance. Prior to analysis, samples (10 mg) were dried to constant weight under 0% rH.

Release experiments were performed under sink conditions in a USP XXIII dissolution apparatus No II (paddle) (Rhône-Poulenc, Paris, France) at 100 rpm and 37±0.5°C in 0.05 M phosphate buffer pH 6.8 dissolution medium. Theophylline concentrations were measured spectrophotometrically using an Ultrospec 4052 TDS apparatus (LKB, Zoetermeer, The Netherlands) at 268 nm. All experiments were carried out in duplicate.

Volume expansion of cylindrical flat-faced PDLA compacts (500 mg, diameter 13 mm, prepared at 190 MPa, hold time 0.1 s) was studied by measuring the dimensions in 0.05 M phosphate buffer pH 6.8 at 37±0.5°C at predetermined time intervals. In addition, axial expansion was measured by thermal mechanical analysis (TMA) with a DMA 2980 in TMA Mode (TA Instruments, New Castle, Delaware, USA) Cylindrical flat-faced PDLA compacts (diameter 9 mm, height ±5 mm, prepared at 157 MPa, hold time 0.1 s) were placed in a specially designed cup (diameter 17 mm, height 8 mm), which could be filled with water. Samples were clamped between the bottom of the cup and an upper parallel plate (diameter 13 mm) (Fig. 1), which exerted a constant force of 0.01 N causing negligible compression at any of the temperatures encountered during testing. Axial tablet expansion was measured as a function of time at constant water temperature until no further increase of the tablet thickness was measured. Furthermore, axial expansion was measured as a function of temperature for both dry and hydrated samples. Dry samples were heated at 2°C/min (under a dry nitrogen purge) whereas hydrated samples were heated at a rate of 0.5°C/min to minimise the delay of the temperature of the water bath. The water temperature was measured with an external thermocouple. The onset temperature ($T_{onset}$) of axial expansion was calculated by extrapolation of the linear part of the deformation recovery curve and determining the point of intersection with the *x*-axis.

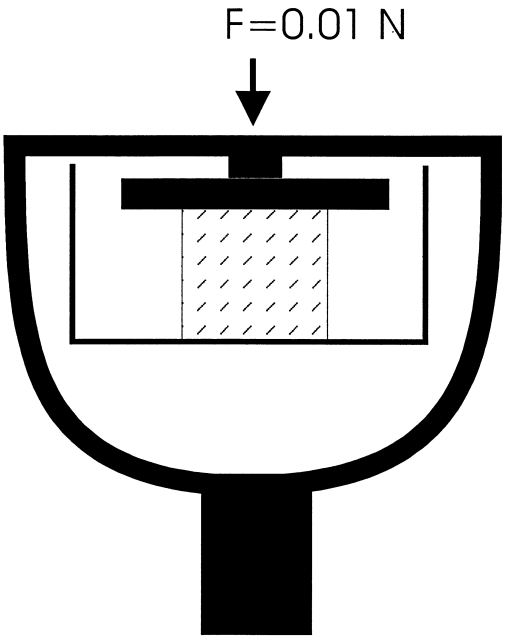


Fig. 1. Schematic representation of the experimental set-up of the thermal mechanical analysis experiments.

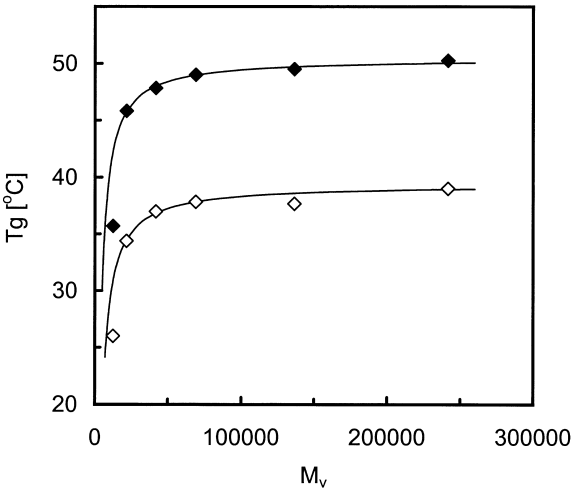


Fig. 2. Effect of molecular weight of poly(DL-lactic acid) on glass transition temperature of dry (♦) and hydrated (37°C water) (◇) PDLA polymers.

## 3. Results and discussion

### *3.1. Glass transition of dry and hydrated PDLA*

Table 1 shows some of the physico-chemical properties of the different viscosity grades of PDLA. The glass transition temperature of dry PDLA powder increased from 35.7°C ($M_v$ $12.5\times10^3$) to 50.2°C ($M_v$ $241.5\times10^3$). In the lower $M_v$ region a rapid increase of $T_g$ was observed, whereas above $M_v$ $69\times10^3$ hardly any further increase of the $T_g$ was observed resulting in a plateau value of approximately 50°C (Fig. 2).

When placed in water (37°C), an immediate reduction of the $T_g$ by 10–11°C was observed for all molecular weight grades of PDLA (Fig. 2). This was in line with the $T_g$ reduction of 12°C of PDLA $M_v$ $85\times10^3$ as reported previously [18] and with data reported in literature [15,17]. However, contrary to PDLA $M_v$ $85\times10^3$, after the initial $T_g$ reduction, the $T_g$ of the hydrated PDLA grades used in this study remained constant for several weeks. This points to rapid absorption of the equilibrium water content, and, since both enthalpy relaxation and monomer release are known to lead to an increase of the $T_g$ (anti-plasticisation) [18], this also points to the absence of enthalpy relaxation and monomer release. The latter was confirmed by pH measurements. Even after several weeks no lowering of the pH of dissolution medium containing the various molecular weight PDLA grades was observed. The different behaviour of the PDLA grades used in this study, is explained by their relatively low residual monomer contents (<1%) as compared with the $M_v$ $85\times10^3$ PDLA of the previous study (4–5%).

The reduction of the $T_g$ is caused by the absorption of water. Experimental quantification of these moisture fractions was difficult. It was impossible to remove all excess surface water from powders collected from dissolution medium and determine the absorbed water content accurately. Therefore, DVS experiments were performed at 37°C and 95% rH to determine the equilibrium moisture fraction of PDLA powder. Although a rH of 95% is not identical to liquid water, a higher rH was technically impossible, but also not desirable since capillary condensation would probably occur. The so-obtained water contents are considered good approximations of the water content sorbed by PDLA in pure water.

Fig. 3 depicts moisture sorption of different molecular weight grades of PDLA at 95% rH. Moisture uptake was small but fast, which was illustrative for

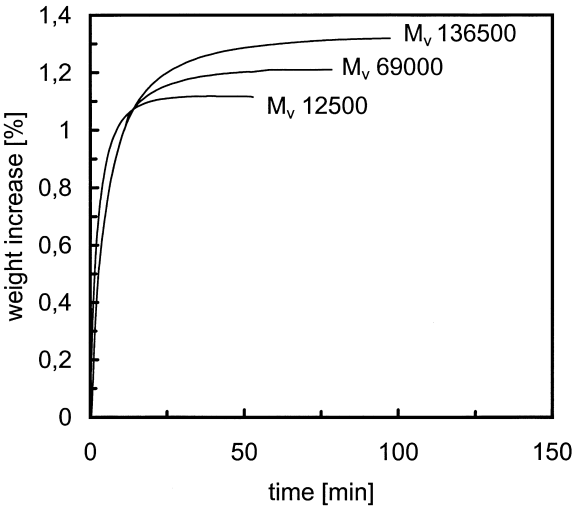


Fig. 3. Sorption profiles of various molecular weight grades of PDLA as determined by dynamic vapour sorption experiments.

the hygroscopic character of the polymers. Although the differences between experimentally determined water fractions were small, $x_w$ appeared to increase slightly with $M_v$, ranging from 1.10% ($M_v$ $21.7\times10^3$) to 1.28% w/w ($M_v$ $136.5\times10^3$). Furthermore, it was observed that the sorption rate decreased with increasing molecular weight. Increasing molecular mobility of PDLA with decreasing $M_v$ and $T_g$ due to which faster diffusion of water molecules through the polymer can occur, is probably responsible for this.

In order to describe the effect of plasticisers on the glass transition temperature of polymers, various relationships have been derived. Sieman [15] reported a good correlation between experimentally obtained $T_g$ values and $T_g$ values calculated with the Couchman–Karasz model [Eq. (1)] for poly(DL-lactic acid) containing small amounts of water [20]:

$$T_g = T_{g,pol} \cdot \exp\left( \frac{x_w \cdot \Delta C_{p,w} \cdot \ln\left(\frac{T_{g,w}}{T_{g,pol}}\right)}{(1-x_w)\cdot \Delta C_{p,pol} + x_w \cdot \Delta C_{p,w}} \right) \quad (1)$$

In Eq. (1), $x_w$ is the fraction water absorbed, and $T_{g,pol}$, $T_{g,w}$ and $T_g$ are the glass transition temperatures of the polymer, water (134 K) and the mixture. $\Delta C_{p,pol}$ and $\Delta C_{p,w}$ are the changes in heat capacity at the $T_g$ of PDLA (0.55 $J\times g^{-1}\ K^{-1}$) and water (1.94 $J\times g^{-1}\ K^{-1}$). The Couchman–Karasz equation is based on a thermodynamic analysis in which the $T_g$ is treated as an Ehrenfest second-order transition and the changes in heat capacity at the $T_g$ in Eq. (1) have to be considered as temperature independent.

The water fractions as theoretically predicted by the Couchman–Karasz equation are listed in Table 2. The average water fraction value was 1.19 (±0.05)% w/w, which corresponds very well with the experimentally obtained average water content of 1.20 (±0.07)% w/w and with other plasticisation data of poly(DL-lactic acid) reported in literature [15] in which a water fraction of 1.2% (gravimetrically determined) caused a reduction of the $T_g$ from 50.1 to 37.6°C. Other theoretical models, which are frequently applied for polymer-plasticizer blends predicted significantly higher moisture fractions. The average water fraction predicted by the modified Couchman–Karasz model derived by Ten Brinke et al. [21] was 1.77 (±0.08)% w/w. The Gordon–Taylor/Kelley–Bueche equation [22], which is frequently applied to describe the glass transition behaviour of homogeneous polymer/plasticiser blends yielded an average moisture fraction of 2.08 (±0.08)% w/w. Finally, by the Fox equation, which is a simplification of the Gordon–Taylor equation and which is generally used for synthetic and

Table 2
Glass transition temperatures of dry and hydrated polymers and moisture contents as determined experimentally with dynamic vapour sorption and predicted with the Couchman–Karasz model

| $M_v$ | $T_g$ (dry) [°C] | $T_g$ (wet) [°C] | $x_w$ (DVS)[a] [%] | $x_w$ ($T_g$)[b] [%] |
|---|---|---|---|---|
| $12.5\times10^3$ | 35.7 | 26.0 | 1.12 | 1.12 |
| $21.7\times10^3$ | 45.8 | 34.4 | 1.10 | 1.23 |
| $41.8\times10^3$ | 47.8 | 37.0 | 1.21 | 1.15 |
| $69.0\times10^3$ | 49.0 | 37.8 | 1.23 | 1.18 |
| $136.5\times10^3$ | 49.5 | 37.7 | 1.28 | 1.25 |
| $241.5\times10^3$ | 50.2 | 39.0 | 1.23 | 1.18 |
| $85.0\times10^3$ | 48.6 | 37.0 | – | 1.23 |
| Mean value[c] (±S.D.) | | | 1.20 (±0.07) | 1.19 (±0.05) |

[a] Equilibrium $x_w$ as determined by DVS (37°C, 95% rH).
[b] $x_w$ as calculated with classical Couchman–Karasz equation.
[c] Mean water fraction and standard deviation for the various $M_w$ polymers.

semisynthetic polymers [22,23] a moisture fraction of 2.62 (±0.09)% w/w was obtained. In conclusion we can state that the classical Couchman–Karasz equation gives the best prediction of the $T_g$ reduction of PDLA. This is in line with results reported by Siemann [15].

### 3.2. Relaxational behaviour of PDLA tablets

Fig. 4 shows the axial expansion of tablets prepared of various molecular weight grades PDLA. The thickness of all tablets except of those prepared of the $M_v$ $12.5\times10^3$ grade, increased rapidly reaching an equilibrium value within a few hours. The data clearly shows that increasing of $M_v$ resulted in a slower but larger axial expansion of the tablets. Axial expansion has previously been related to the recovery of the pre-compaction state of the individual powder particles [18]. It was concluded that this 'shape memory behaviour' is caused by entropy-driven relaxation of deformed polymer particles when the glassy polymer changes to the rubbery state. Upon compaction, polymer chains are forced to adapt a different conformation, which leads to lowering of the entropy and since $\Delta G=\Delta H-T\Delta S$, to an increase of the Helmholtz free energy [18]. Upon removal of the applied stress and storage of the tablets, this deformed state is frozen due to the limited mobility of the polymer chains below $T_g$. During storage below $T_g$, enthalpy relaxation will occur [24–27] which involves the relaxation of relatively small molecular groups with sufficient mobility (small relaxation times). This process, which is also called physical ageing [28] might lead to small dimensional changes of the samples and its rate depends on storage temperature and molecular weight [24]. Other studies have shown that volumetric recoveries can occur at the glass transition temperature during heating of powder samples after storage below $T_g$ [29].

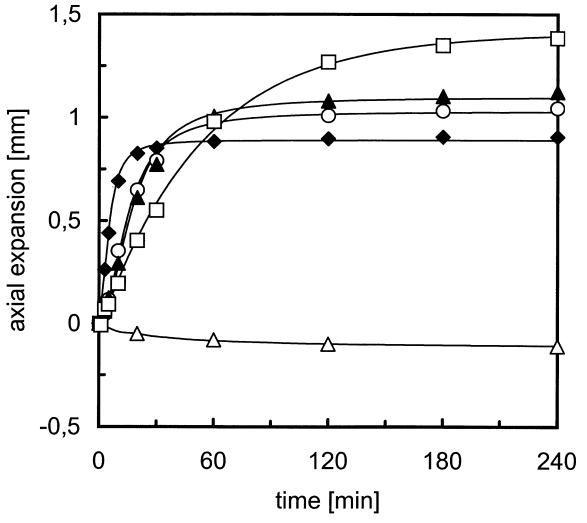


Fig. 4. Influence of molecular weight on axial expansion of PDLA tablets in aqueous dissolution medium of 37°C. Molecular weights ($M_v$) are: 12,500 (△), 21,700 (♦), 41,800 (○), 136,500 (▲) and 241,500 (□).

Upon increasing of the temperature or lowering of the glass transition (or a combination of both), the time-scale of the largest molecular motions is dramatically lowered. Near or above $T_g$, these motions contribute to a decrease of the free energy. Macroscopically, this results in recovery of the pre-compaction conformation of individual polymer chains and axial expansion of the tablets in 37°C water [18].

In analogy with the description of an enthalpy recovery process during storage, the axial expansion of PDLA tablets in water at temperatures exceeding $T_{g,wet}$ was described by the following empirical relationship:

$$\phi_t = \exp\left(-\frac{t}{\tau}\right)^{\beta} \quad (2)$$

where $\phi_t$ is the degree of relaxation, $\tau$ is the mean relaxation time (which is the time required for a single molecular motion of a particular type to occur [24]) and $\beta$ is a relaxation time distribution parameter ($0<\beta<1$). $\beta$ values lower than unity indicate that a distribution of relaxation times is required for an accurate description of the total relaxational process. The maximum extent of relaxation depends on the extent of deformation during the compaction process. Complete recovery of the pre-compaction thickness of the powder compacts will be equivalent to a relaxation degree of unity. Therefore, macroscopically, the degree of relaxation is represented by:

$$\phi_t = \frac{\Delta h_t}{\Delta h_\infty} \quad (3)$$

where $\Delta h_t$ is the increase of the tablet thickness after

a certain period and $\Delta h_\infty$ the maximum increase of the tablet thickness.

The parameters $\tau$ and $\beta$ were obtained by using non-linear regression curve fitting of the experimental axial expansion data according to Eqs. (2) and (3). $\beta$ values ranged from 0.79 to 0.98. Fig. 5 shows that $\tau$ increases with molecular weight, which is in line with the results from ageing studies with polystyrene which showed that $\tau$ increased with increasing molecular weight when the studies were performed at the same experimental temperature [25]. Fig. 6, which also includes data obtained from volume expansion experiments of $M_v$ $85\times10^3$ PDLA tablets at different water temperatures [18], shows that $\tau$ increases with increasing values of $T_g-T$. The mean relaxation times of $M_v$ $85\times10^3$ PDLA tablets decreased with increasing water temperature. The relaxation times of different molecular weight grades of PDLA can be superimposed when the temperature intervals $T_g-T$ are the same, which is in line with enthalpy relaxation data of polystyrene [30]. The effect of temperature on $\tau$ was non-linear and significantly greater than could be predicted by a simple logarithmic relationship, a behaviour similar to that of poly(vinylpyrrolidone) [24]. The experimental results clearly show that $\tau$ increases within a relatively narrow temperature range from minutes (above $T_g$) to nearly half a day ($T_g-T=$ 6°C).

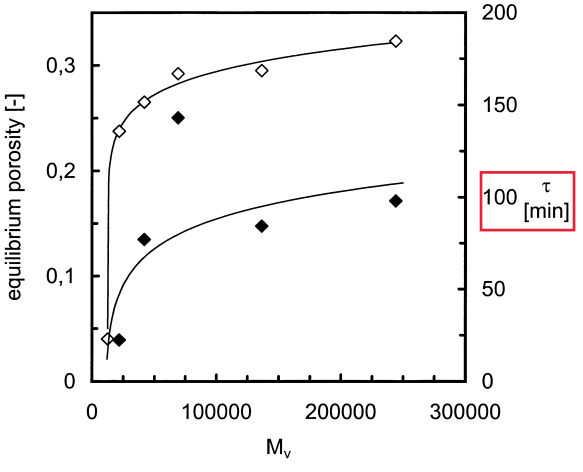


Fig. 5. Effect of molecular weight on equilibrium porosity (◇) and mean relaxation time $\tau$ (♦) of PDLA tablets.

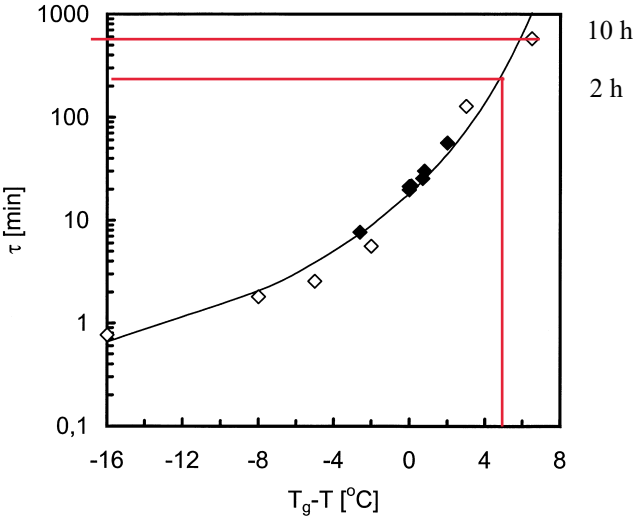


Fig. 6. Relaxation times of PDLA tablets versus normalised temperature $T_g-T$. The graph includes $\tau$ values as determined from expansion experiments with different molecular weight grades of PDLA performed at 37°C (♦) and $\tau$ values as determined from expansion experiments of $M_v$ 85,000 PDLA at different water temperatures [18] (◇).

### 3.3. Thermal mechanical analysis measurements

Fig. 7 shows the axial expansion of different molecular weight PDLA tablets during heating at 0.5 K/min. For ease of comparison, the data are plotted versus the temperature interval $T-T_g$. These S-shape curves are also called the integral deformation recovery curves or integral curves of the memory effect [31]. In the lower temperature range hardly any recovery was observed, but as the temperature increased, at a certain value, called the onset temperature ($T_{onset}$), the tablet height rapidly increased up to a maximum value. Irrespective of molecular weight, $T_{onset}$ values of dry PDLA tablets (Fig. 7, left) were slightly higher than the $T_g$ of the polymers (Table 3). During the first part of the recovery curves, just above $T_g$, hardly any effect of molecular weight on recovery behaviour was observed. However, upon further increasing the temperature, large differences were observed. Expansion behaviour of PDLA tablets in water (Fig. 7, right) was similar to that of dry tablets. $T_{onset}$ values were close to the $T_g$ of the hydrated polymers (Table 3). Except for the lowest molecular weights, axial expansion of hy-

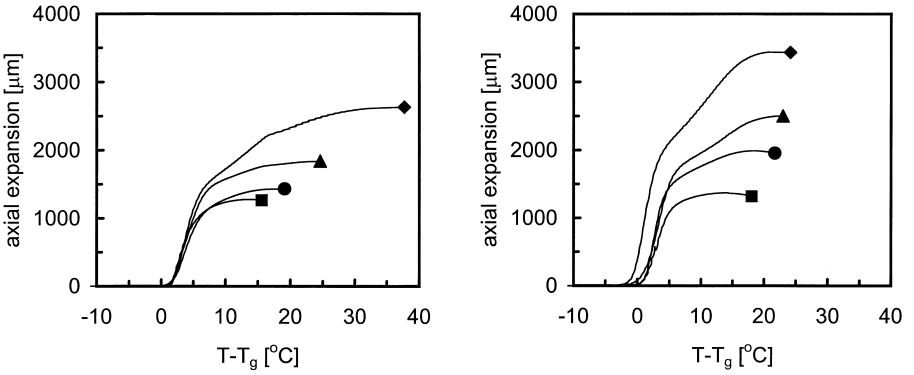


Fig. 7. Thermally stimulated deformation recovery curve of dry (left) and hydrated (right) PDLA compacts versus scaled temperature $T - T_g$. Molecular weights ($M_v$) of the PDLA grades used were: 21,700 (■), 41,800 (●), 69,000 (▲) and 241,500 (♦).

drated tablets was considerably larger than that of dry tablets. The reason for this is probably that the presence of water weakens interparticle bonding. Furthermore, porous compacts are filled with water, which prevents the tablet from collapsing. The maximum expansion was found to be highly dependent on molecular weight, which was in line with the time-expansion curves shown in Fig. 4. This is also shown in Table 3 where the maximum expansion is listed as the relative expansion degree, $h_{max}/h_0$.

Fig. 8 shows the integral expansion curves of dry and hydrated PDLA compacts with $M_v$ $21.7\times10^3$ and $M_v$ $241.5\times10^3$. The graphs clearly show the shift of the curves to a lower temperature range due to plasticisation of PDLA by water. The reduction of $T_{onset}$ by approximately 12–13°C was in line with data obtained from modulated DSC. Furthermore, Fig. 8 shows the corresponding differential deformation recovery curves. The peak of these curves represents the temperature ($T_{max}$) at which the recovery rate, $v_{max}$ has its maximum value. The differential recovery curves of high molecular weight

Table 3
Characteristic parameters of shape recovery of dry and hydrated PDLA tablets (heating rate 0.5°C/min, $h_0 \approx 4.7$ mm)

| $M_v$ | $T_g$ (°C) | $T_{onset}$ (°C) | $T_{max}$ (°C) | $v_{max}$ (µm/K) | $h_{max}/h_0^a$ (–) |
|---|---|---|---|---|---|
| *Dry PDLA tablets* | | | | | |
| $12.5\times10^3$ | 35.7 | – | – | – | – |
| $21.7\times10^3$ | 45.8 | 47.4 | 48.4 | 321.3 | 0.282 |
| $41.8\times10^3$ | 47.8 | 49.7 | 51.2 | 272.2 | 0.306 |
| $69.0\times10^3$ | 49.0 | 51.0 | 52.2 | 312.2 | 0.387 |
| $136.5\times10^3$ | 49.5 | 51.1 | 52.2 | – | – |
| $241.5\times10^3$ | 50.2 | 51.3 | 52.5 | 375.3 | 0.558 |
| *Hydrated PDLA tablets* | | | | | |
| $12.5\times10^3$ | 26.0 | – | – | – | – |
| $21.7\times10^3$ | 34.4 | 35.4 | 37.7 | 309.9 | 0.291 |
| $41.8\times10^3$ | 37.0 | 37.8 | 39.2 | 435.0 | 0.423 |
| $69.0\times10^3$ | 37.8 | 37.6 | 40.2 | 418.1 | 0.533 |
| $136.5\times10^3$ | 37.7 | 37.9 | 40.3 | 432.0 | 0.611 |
| $241.5\times10^3$ | 39.0 | 38.3 | 40.3 | 552.8 | 0.731 |

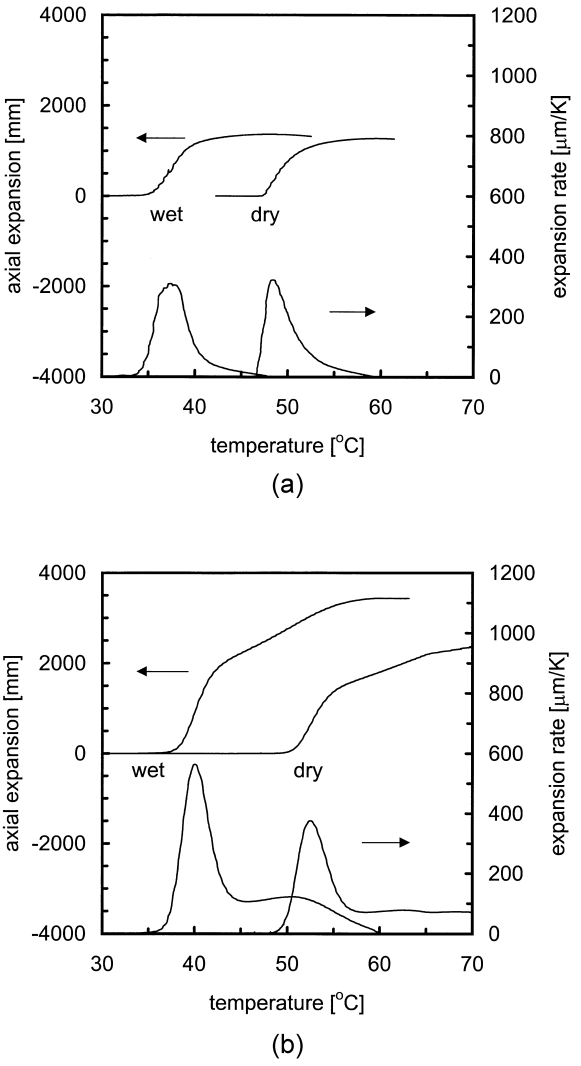


Fig. 8. Thermally stimulated deformation recovery curve of dry and hydrated compacts with $M_v$ 21,700 (a) and $M_v$ 241,500 (b). The curves in the upper part represent the integral recovery curves, whereas the curves in the lower part represent the differential recovery curve.

PDLA tablets exhibited a second peak or shoulder around 50°C, corresponding with the $T_g$ of dry PDLA. This is probably caused by incomplete wetting of the compacts during the expansion experiments.

The recovery parameters in Table 3 show some interesting phenomena. Both $T_{onset}$ and $T_{max}$ increased with molecular weight. The onset temperature is generally recognised as the softening temperature and it was therefore not surprising that $T_{onset}$ values resembled $T_g$ values quite well. The increase of $v_{max}$ with molecular weight is more difficult to understand. In the previous section we showed that $\tau$ increased with molecular weight and more specific with the temperature interval $T_g - T$. The recovery rate $v_{max}$ was found to decrease with increasing $T_g - T$. This would mean that the relaxation time ($\tau$) increased with increasing $T_g - T$, which is in contrast to what we observed in the previous paragraph. The latter could be explained by the relatively larger entropy reduction of higher molecular weight PDLA as a result of compaction (long polymer chains do not respond (relax) to the compressional force as fast as short polymer chains do) and the lower extent of enthalpy relaxation of higher molecular weight PDLA during storage. Since the 'entropy spring' is the driving force in the volume expansion of PDLA compacts, a larger entropy reduction during compaction may lead to a larger value of $v_{max}$. The lack of expansion of tablets of $M_v$ $12.5\times10^3$ tablets can be explained by the molecular weight between entanglements ($M_e$) of PDLA. $M_e$ is one of the most important parameters in determining the mechanical properties of polymers below $T_g$. Entanglements act as physical crosslinks and the lower the number of physical crosslinks, the less elastic the polymer will behave. To possess sufficient mechanical strength, the molecular weight of polymers should be at least a number of times that of $M_e$. For the PDLA grade used in this study, a value of approximately $6.0\times10^3$ has been reported for $M_e$ [32]. The entanglement density of $M_v$ $12.5\times10^3$ PDLA is too low to give the polymer sufficient mechanical strength and elasticity (memory). In water, the lack of entanglements was expressed by the absence of shape recovery since, upon plasticisation by water, the polymer acts more like a viscous liquid rather than an elastic rubber.

### 3.4. Release characteristics

Water uptake is the first step in the overall mechanism of drug release from tablets. Taking into account the role of molecular relaxation in the mechanism of water uptake, it was expected that the

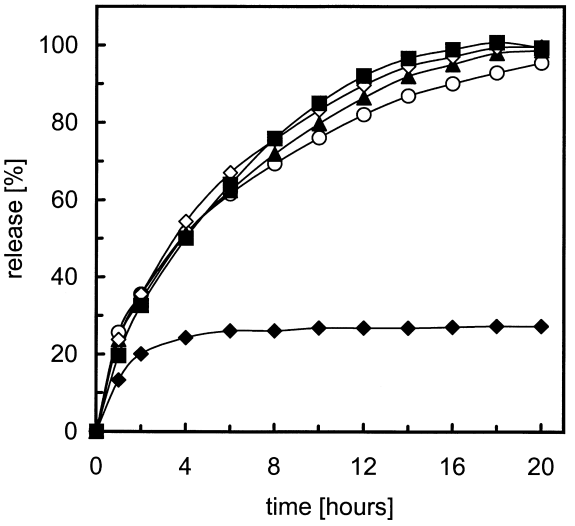


Fig. 9. Theophylline release from tablets (200 mg, ∅ 9 mm, 20% w/w theophylline) prepared of PDLA powders with molecular weights of: 12,500 (♦), 21,700 (○), 69,000 (▲), 136,500 (◇) and 241,500 (■).

molecular weight of the polymer would affect water uptake and consequently drug release of PDLA tablets. However, as is shown in Fig. 9, contrary to expansion behaviour, theophylline release from PDLA tablets was only slightly affected by molecular weight (except for $M_v$ $12.5\times10^3$). Release of theophylline from tablets containing $M_v$ $12.5\times10^3$ PDLA was incomplete due to the lack of volume expansion and water uptake of these tablets. Due to the low viscosity of the plasticised polymer, tablet pores were blocked and the majority of the drug particles became trapped in the viscous polymer matrix. Release of theophylline was analysed according to the general equation:

$$\frac{M_t}{M_\infty} = kt^n \tag{4}$$

in which $M_t/M_\infty$ is the fractional release, $k$ is a constant characteristic of the system, and $n$ is an exponent characteristic of the mode of transport of the solute. The parameters $n$ and $k$ were calculated by means of non-linear regression curve fitting of the experimental release data according to Eq. (4) (Table 4). The calculated $n$-values ranged from 0.50 to 0.62, which points to a Fickian or diffusion controlled transport mechanism [33]. The small increase of the overall release rate with molecular weight is caused by the larger expansion degree (higher equilibrium porosity) of tablets prepared of high molecular weight PDLA. Although expansion of low molecular weight compacts is faster, the final porosity (reached within 2 h) is lower. Since release occurs over a period of 16–24 h, the equilibrium 'porosity' is much more important for the release rate than the 'rate' of expansion. The $n$-values also increased with $M_v$. Low $M_v$ PDLA tablets expand rapidly, and expansion will be complete within a short period (Fig. 4). The major part of the incorporated drug will be released from a nearly inert matrix and consequently $n$ is close to 0.5. Slower relaxation of high molecular weight PDLA results in a porosity increase over an extended period (up to 4 h, Fig. 4). As a result, the effective diffusion coefficient increases during an extended period which results in a smaller decline of the release rate with time (and consequently larger $n$-values).

Table 4
Analysis of theophylline release data[a]

| $M_v$ | $n$ | $k$ | $r^2$ |
|---|---|---|---|
| $12.5\times10^3$ | – | – | – |
| $21.7\times10^3$ | 0.500 | 0.2547 | 0.9978 |
| $41.8\times10^3$ | 0.535 | 0.2475 | 0.9980 |
| $69.0\times10^3$ | 0.546 | 0.2379 | 0.9985 |
| $85.0\times10^3$ | 0.534 | 0.2343 | 0.9989 |
| $136.5\times10^3$ | 0.570 | 0.2435 | 0.9977 |
| $241.5\times10^3$ | 0.618 | 0.2122 | 0.9988 |

[a] $n$, kinetic exponent, $k$, system constant.

However, the effect of molecular weight on drug release from tablets containing 20% w/w theophylline was marginal compared to the effect on volume expansion. This is caused by the fact that tablets containing 20% w/w theophylline expand to a lesser extent than tablets which consist of 100% PDLA. Furthermore, a significant fraction of the pores is created by dissolution of the volume fraction drug, which is identical for all PDLA tablets. It might be expected that drug release from lower-dosed tablets will be influenced by molecular weight to a larger extent.

## 4. Conclusion

Comparison of dynamic vapour sorption and theoretical models predicting the $T_g$ of polymer-diluent blends showed that water fractions of approximately 1.2% were responsible for the observed reduction of the $T_g$ by 10–12°C. Volume expansion studies using TMA showed that the molecular relaxation time and equilibrium porosity of the tablets increased with molecular weight. The expansion behaviour of PDLA tablets could be relatively well described by a relaxational model adapted from enthalpy relaxation models. The mean relaxation time calculated by non-linear regression fitting of the expansion data according to this model increased exponentially with the temperature interval $T_g - T$. TMA showed to be an effective technique to investigate the shape memory behaviour of PDLA tablets. It clearly illustrated the effect of molecular weight of PDLA on the relaxation behaviour of the tablets.

The onset temperature of shape recovery of hydrated tablets was approximately 12–13°C lower than for dry samples, which corresponded with the $T_g$ reduction mentioned before. Expansion studies showed that the maximum expansion degree was largely dependent on molecular weight. However, despite of the effect of molecular weight on volume expansion behaviour of PDLA tablets, drug release was only slightly affected by molecular weight at a drug load of 20% w/w theophylline monohydrate.

## Acknowledgements

The authors would like to thank PURAC Biochem (Gorinchem, The Netherlands) and Hycail (Noordhorn, The Netherlands) for kindly supplying the various molecular weight grades poly(DL-lactic acid).

## References

[1] D.E. Cutright, J.D. Beasley, B. Perez, Histologic comparison of polylactic and polyglycolic acid sutures, Oral Surg. 32 (1971) 165–173.
[2] D.E. Cutright, E.E. Hansuck, The repair of fractures of the orbital floor using biodegradable polylactic acid, Oral Surg. 33 (1972) 28–34.
[3] I. Yamakawa, M. Kawahara, S. Watanaba, Y. Miyake, Sustained release of insulin by double-layered implant using poly(DL-lactic acid), J. Pharm. Sci. 79 (6) (1989) 505–509.
[4] S. Cohen, T. Yoshioka, M. Lucarelli, L.H. Hwang, R. Langer, Controlled delivery system for proteins based on poly(lactic/glycolic acid) microspheres, Pharm. Res. 8 (6) (1991) 713–720.
[5] R. Jalil, J.R. Nixon, Biodegradable poly(lactic acid) and poly(lactide-co-glycolide) microcapsules: problems associated with preparative techniques and release properties, J. Microencapsul. 7 (3) (1990) 297–325.
[6] M.O. Omelczuk, J.W. McGinity, The influence of polymer glass transition and molecular weight on drug release from tablets containing poly(DL-lactic acid), Pharm. Res. 9 (1) (1992) 26–32.
[7] M.O. Omelczuk, J.W. McGinity, A comparative investigation of the compaction and dissolution properties of tablets containing poly(DL-lactic acid) as a binder and retardant polymer, S.T.P. Pharm. Sci. 5 (3) (1995) 181–186.
[8] K. Avgoustakis, J.R. Nixon, Biodegradable controlled release tablets: III. Effect of polymer characteristics on drug release from heterogeneous poly(lactide-co-glycolide) matrices, Int. J. Pharm. 99 (1993) 247–252.
[9] B. Korsatko-Wabnegg, W. Korsatko, Vergleich der Formulierungs- und Retardierungseigenschaften Biodegradabler Polyhydroxyalkanoate zur Herstellung von Matrixformulierungen, Sci. Pharm. 57 (1989) 317–323.
[10] F. Moll, G. Köller, Biodegradable tablets having a matrix of low-molecular weight poly-L-lactic acid and poly-DL-lactic acid, Arch. Pharm. 323 (1990) 887–888.
[11] R. Mank, H. Kala, M. Richter, Darstellung peroraler Retardarzneiformen auf der Basis von biologisch abbaubaren Polymeren. 2. Mitteilung: Darstellung von Matrixtabletten auf der Basis von Polymilchsäure, Pharmazie 44 (1989) 328–330.
[12] C.J. Brine, Process for polymerizing poly(lactic acid), U.S. Patent 5075115, December 24, 1991.
[13] J.W. McGinity, K.T. Chang, Method for preparing a solid sustained release form of a functionally active composition and the dosage form so obtained, WO 89/04673, June 1, 1988.
[14] R. Steendam, C.F. Lerk, Poly(DL-lactic acid) as a direct compression excipient in controlled release tablets. Part I. Compaction behaviour and release characteristics of poly(DL-lactic acid) tablets, Int. J. Pharm. 175 (1998) 33–46.
[15] U. Siemann, The influence of water on the glass transition of poly(DL-lactic acid), Therm. Acta 85 (1985) 513–516.
[16] C.G. Pitt, Z.W. Gu, Modification of the rates of chain cleavage of poly(ε-caprolactone) and related polyesters in the solid state, J. Control. Rel. 4 (1987) 283–292.
[17] S.S. Shah, Y. Cha, C.G. Pitt, Poly(glycolic acid-co-DL-lactic acid): diffusion or degradation controlled drug delivery?, J. Control. Rel. 18 (1992) 261–270.
[18] R. Steendam, H.W. Frijlink, C.F. Lerk, Poly(DL-lactic acid)

as a direct compression excipient in controlled release tablets. Part II. Plasticisation and water-induced shape memory behaviour of poly(DL-lactic acid) (in preparation).
[19] R. Steendam, H.W. Frijlink, C.F. Lerk, Poly(DL-lactic acid) as a direct compression excipient in controlled release tablets. Part III. The role of shape memory phenomena in water uptake and drug release of poly(DL-lactic acid) tablets (in preparation).
[20] P.R. Couchman, F.E. Karasz, A classical thermodynamic discussion of the effect of composition on glass transition temperatures, Macromolecules 11 (1978) 1156–1161.
[21] G. Ten Brinke, F.E. Karasz, T.S. Ellis, Depression of glass transition temperatures of polymer networks by diluents, Macromolecules 16 (1983) 244–249.
[22] B.C. Hancock, G. Zografi, The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids, Pharm. Res. 11 (4) (1994) 471–477.
[23] T.G. Fox, P.J. Flory, Second-order transition temperatures and related properties of polystyrene. I. Influence of molecular weight, J. Appl. Phys. 21 (1950) 581–591.
[24] B.C. Hancock, S.L. Shamblin, G. Zografi, Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures, Pharm. Res. 12 (6) (1995) 799–805.
[25] S.R. Jong, J.S. Lee, T.L. Yu, Physical ageing of poly(ether sulfone) from enthalpy relaxation measurements, Macromol. Chem. Phys. 198 (1997) 2373–2386.
[26] A. Brunacci, J.M.G. Cowie, R. Ferguson, I.J. McEwen, Enthalpy relaxation in glassy polystyrenes, Polymer 38 (4) (1997) 865–870.
[27] J.M.G. Cowie, R. Ferguson, Physical ageing of poly(methyl methacrylate) from enthalpy relaxation measurements, Polymer 34 (10) (1993) 2135–2141.
[28] T.A. Tervoort, Constitutive modelling of polymer glasses. Finite, non-linear viscoelastic behaviour of polycarbonate. PhD thesis, Eindhoven University of Technology (1996) 141.
[29] E. Fukuoka, M. Makita, Y. Nakamura, Glassy state of pharmaceuticals. 4. Studies on glassy pharmaceuticals by thermochemical analysis, Chem. Pharm. Bull. 37 (1989) 2782–2785.
[30] A. Agrawal, Effect of temperature and molecular weight on enthalpy relaxation in polystyrene, J. Pol. Sci. Polym. Phys. 27 (7) (1989) 1449–1461.
[31] X. Luo, X. Zhang, M. Wang, D. Ma, M. Xu, F. Li, Thermally stimulated shape-memory behavior of ethylene oxide-ethylene terephtalate segmented copolymer, J. Appl. Pol. Sci. 64 (12) (1997) 2433–2440.
[32] D.W. Grijpma, Chain entanglement, mechanical properties and drawability of poly(lactide), Colloid Polymer Sci. 272 (9) (1994) 1068–1081.
[33] F. Carli, L. Simioni, Kinetics of liquid capillary penetration into inert polymer matrices, Pharm. Acta Helv. 53 (11) (1978) 320–326.