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International Journal of Pharmaceutics 175 (1998) 33–46

international journal of pharmaceutics

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) matrix tablets

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Received 11 November 1997; received in revised form 15 July 1998; accepted 19 July 1998

Abstract

High-molecular weight poly(DL-lactic acid) (PDLA, M_v 85000) was applied as a direct compression excipient in controlled release tablets. PDLA powders with good flowing properties were obtained by milling pre-cooled PDLA granules. Apparent yield pressure values ranged from 44 to 71 MPa for tabletting speeds of 0.033 and 300 mm/s, respectively, pointing to a high ductility and limited strain rate sensitivity. Tablets with good mechanical strength (tensile strength 2.5–3.7 MPa) were prepared at different compaction speeds. Dissolution experiments with different drugs showed that PDLA exhibited good sustained release properties. Initial tablet porosity, lubrication with magnesium stearate and pH of the dissolution medium hardly affected the release rate of the incorporated drug. Drug loads, however, markedly affected the release rate. For drug loads between 20 and 50% w/w, a constant fractional release rate was found. Upon further decreasing of the drug load, the release rate was found to increase. This remarkable finding was explained by the rapid and large increase of the pore volume of the tablets. The results show the unique properties of PDLA and its suitability to be applied as a direct compression and release controlling excipient in matrix tablets for oral drug administration.

Keywords: Poly(DL-lactic acid); Matrix tablets; Direct compression; Compaction speed; Porosity; Controlled release

1. Introduction

Poly(DL-lactic acid) (PDLA) and related polymers have been extensively investigated for use in medical and pharmaceutical devices (Cutright et

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0378-5173/98/$ - see front matter
PII S0378-5173(98)00242-7

al., 1971; Cutright and Hansuck, 1972). Current pharmaceutical investigations using PDLA have focused on potential applications for implantable sustained release systems (Yamakawa et al., 1989), microspheres (Cohen et al., 1991) and microcapsules (Jalil and Nixon, 1990). During the last decade, an increasing number of papers and patents reported the application of PDLA as a sustained release excipient in tablets. In several studies, a wet granulation method was part of the process to prepare matrix tablets with PDLA as a retardant. By granulation of an aqueous latex dispersion (Coffin et al., 1987) or an organic solution (Chang et al., 1987) of the polymer with a blend of the active ingredient and excipient(s), only 5–15% w/w PDLA was required to prepare tablets with good mechanical and retardant properties. Polymer properties such as the glass transition temperature and molecular weight (Omelczuk and McGinity, 1992) and thermal treatment of the tablets (Omelczuk and McGinity, 1993, 1995) significantly affected the mechanical properties of the tablets and release of the incorporated drug. Other studies reported the use of spray-dried PDLA in controlled release tablets (Avgoustakis and Nixon, 1993a,b). Spray-drying of very dilute solutions of PDLA yielded very ductile powders with good compaction properties.

Compared to processes which require a granulation step, direct compression offers major advantages (Paronen et al., 1995; Armstrong, 1997). Consequently, direct compression is one of the most popular techniques to prepare (controlled release) tablets. Only a few commercial excipients are well adapted for direct compression into controlled release formulations. Therefore, considerable research has been done on the development of direct compression excipients and interest still continues.

PDLA has also been investigated for its suitability as a direct compression excipient in sustained release tablets. Low molecular weight PDLA (M_W 6000) prepared by direct polyesterification of lactic acid, exhibited good compaction (Mank et al., 1989a) and interesting release controlling properties (Mank et al., 1989b). However, as a result of its low molecular weight, considerable hydrolytic degradation of the polymer during dissolution experiments was observed. Because drug release from tablets containing low molecular weight PDLA (M_W 2000) was also highly pH dependent (Moll and Köller, 1990), it was concluded that low molecular weight PDLA was not suitable for peroral application.

Ring-opening polymerisation of DL-dilactide yields PDLA with a considerably higher molecular weight (Grypma, 1993). Due to the higher molecular weight, the polymer exhibits a higher glass transition temperature (Omelczuk and McGinity, 1992) and a smaller number of free carboxyl end groups. Consequently, degradation of high molecular weight PDLA in aqueous media is relatively slow when compared to low molecular weight PDLA. Until now, attempts to use high molecular weight PDLA (M_W 25000) as a release controlling excipient in tablets prepared by direct compression were not successful as mechanical grinding of the polymer was not possible and PDLA powder prepared by freeze-drying exhibited very poor flowing properties (Mank et al., 1989a). A further increase of the glass transition temperature (by increasing the molecular weight) or cooling of the polymer is expected to facilitate grinding of PDLA.

In the present study, cryogenic milling was applied as a method to grind high molecular weight PDLA (M_v 85000) granules. The primary objective of this investigation was to study the suitability of high molecular weight PDLA as a release controlling excipient in tablets prepared by direct compression. A compaction simulator was used to study the compaction properties of mechanically milled PDLA at different tabletting speeds. Several drugs were incorporated in the tablets and the influence of drug load and porosity on release of drug from the matrix tablets was studied.

2. Materials and methods

2.1. Materials

Poly(DL-lactic acid) (PDLA) containing 25% D-lactide and 75% L-lactide and prepared by ring-opening polymerisation of DL-dilactide was ob-

tained from Hycail (Noordhorn, The Netherlands). Polymerisation was carried out in a batch-reactor (140–180°C) with stannous octoate (0.1 w/w %) as a catalyst. Subsequently, the polymer was melt-extruded and chopped into small granules. The percentage of unreacted monomer as determined by nuclear magnetic resonance (Grypma, 1993) was 4.7%. The intrinsic viscosity (chloroform, 25°C, Ubbelohde viscosimeter) was 1.44 dl/g. Application of the Mark–Houwink relation using $K = 2.28 \times 10^{-4}$ and $a = 0.771$ yielded a viscosity averaged molecular weight (M_v) of 85000. 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. Prednisolone, theophylline monohydrate, (Genfarma, Maarssen, The Netherlands) and paracetamol (Bufa-Chemie, Castricum, The Netherlands) were used as model drugs. Magnesium stearate and ethyl cellulose (Ethocel® FP 7 cPs) were obtained from Centrachemie (Etten–Leur, The Netherlands) and Dow (Midland, MI), respectively. Microcrystalline Cellulose (Pharmacel® 101) was obtained from DMV International (Veghel, The Netherlands). Pregelatinised spray-dried potato starch (Paselli® WA4) was supplied by Avebe (Foxhol, The Netherlands). All excipients, except PDLA and the drugs used were stored under ambient conditions (22°C, R.H. 55%). The cumulative particle size distribution of all relevant tablet components was measured with a laser diffraction spectrometer (Helos 12LA, Sympatec, Clausthal, Germany) containing a 200 mm lens and using Fraunhofer's theory. The powders were dispersed at a pressure of 4 bar with a Sympatec Rodos dry disperser. The results are given in Table 1. The true densities of PDLA and theophylline monohydrate measured at 22°C by a helium pycnometer MVP-1 (Quantachrome, Syosset, NY) were 1.244 and 1.460 g/cm^3, respectively. The angle of repose of PDLA powder was determined by measuring the height of a powder heap with a diameter of 5 mm by means of a cathetometer. The Hausner ratio as determined from the bulk and tapped density was determined according to DIN 53194.

2.2. Compaction behaviour of PDLA

The compaction behaviour of PDLA powder was studied on a high-speed compaction simulator (ESH, Brierley Hill, UK). Flat-faced compacts of 100% PDLA (diameter 13 mm, 500 mg) were prepared at different compaction speeds (0.033, 3, 30 and 300 mm/s). Before each compression, the die was lubricated with magnesium stearate. Upper punch displacement profiles were sine waves with different amplitudes in order to reach different maximum compaction pressures. The lower punch was stationary during compression. Both the upper punch displacement and force were recorded. Heckel plots (Heckel, 1961a,b) were derived from at pressure porosities of the compacts under pressure and the applied pressures, as determined from the force–displacement data. The various kinds of compression work were calculated by integrating the force–displacement curves, using a computer programme. After at least 16 h relaxation (22°C, R.H. 55%), tablets were weighed with an accuracy of 0.1 mg on an analytical balance (Mettler, Zürich, Switzerland) and diameter and height were measured with a micrometer. The crushing strength of the tablets was determined with a Schleuniger Instrument Model 2E (Dr. K. Schleuniger, Zürich, Switzerland). The tensile strength (τ_c) of the tablets was calculated from the crushing strength (F_c) according to:

Table 1
Particle size distribution of tablet components

Compound	d^a_{10} (μm)	d^a_{50} (μm)	d^a_{90} (μm)
PDLA	72	146	223
PDLA[b]	162	215	279
Ethocel®	11	40	77
Pharmacel 101	23	51	88
Paselli WA4	49	209	427
Prednisolone	4.0	22	61
Theophylline	9.3	33	72
Paracetamol	5.4	41	155

[a] Diameters representing cumulative powder volume up to 10, 50 and 90% respectively (undersize curve).
[b] PDLA powder (sieve fraction 180–250 μm) used in tablets for electron microscopy photographs.

$$\tau_c = \frac{2F_c}{\pi dh} \quad (1)$$

in which d and h are the diameter and thickness of the tablets.

Specific surface area of PDLA powder and tablets (100% PDLA) prepared at different compaction pressures (compaction speed 3 mm/s) was determined by nitrogen adsorption in a Quantasorp gas adsorption apparatus (Quantachrome, Syosset, USA) according to the BET method.

2.3. Preparation and characterisation of the PDLA/drug compacts

Physical mixtures of PDLA/theophylline monohydrate, PDLA/prednisolone and PDLA/paracetamol were prepared by mixing the compounds in a Turbula mixer (Bachoven, Basle, Switzerland) at 90 rpm for 30 min. No additional compounds were added. Cylindrically flat-faced PDLA compacts (500 mg, diameter 13 mm) containing 200 mg drug were prepared on a hydraulic press (ESH Testing, Brierley Hill, UK) at 188 MPa and a load rate of 7.5 MPa/s. The maximum compaction pressure was held for 0.1 s. To investigate the effect of drug load on drug release, PDLA tablets (500 mg, diameter 13 mm) containing 20–400 mg theophylline monohydrate were prepared at 188 MPa (load rate 7.5 MPa/s, hold time 0.1 s). The drug load was expressed as drug weight per tablet weight. To study the effect of initial porosity on drug release, PDLA tablets (500 mg, diameter 13 mm) containing 100 mg theophylline monohydrate were prepared at compaction pressures ranging from 30 to 300 MPa (load rate 7.5 MPa/s, hold time 0.1 s). Porosities of the tablets were calculated from the weight and dimensions of the tablets and the true densities of the powders.

2.4. Study of the tablet surface by scanning electron microscopy

Electron micrographs were made of vacuum dried samples using a scanning electron microscope (Jeol JSM-U3, Japan) operating at 1.5 kV. Prior to investigation, the samples were sputter-coated with Au–Pd.

2.5. Dissolution studies

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 or in 0.1 N HCl pH 1 dissolution medium. The drug concentrations were measured spectrophotometrically using an Ultrospec 4052 TDS apparatus (LKB, Zoetermeer, The Netherlands) at 268 nm for theophylline monohydrate, 248 nm for prednisolone and 243 nm for paracetamol. All experiments were carried out in duplicate.

The total pore volume of PDLA tablets containing different theophylline loads after 2 h of immersion in 0.05 M phosphate buffer pH 6.8 at 37 ± 0.5°C was calculated from the weight and dimensions of the tablets, the true densities of PDLA and theophylline, and the amount of drug released after 2 h.

3. Results and discussion

3.1. Compaction experiments

The SEM photograph in Fig. 1a shows PDLA powder, which was prepared by cryogenic grinding of PDLA granules. The amorphous powder exhibited good flowability (angle of repose 40°, Hausner ratio 1.25), which is an important characteristic for a potential direct compression excipient. The free flowing properties are attributed to the non-porous character and smooth surface of the particles and the rather uniform particle size and shape. The non-porous character of the particles is further demonstrated by the low specific surface area of 0.15 m^2/g.

PDLA exhibits a highly ductile character, which is illustrated by the SEM photograph in Fig. 1b, which displays the surface morphology of a PDLA tablet compacted at a pressure of 190 MPa. Comparison of Fig. 1a with Fig. 1b clearly shows the high degree of plastic deformation of the particles as a result of compression. Despite the fact that the particles have lost their original pre-compaction shape and particle surfaces are

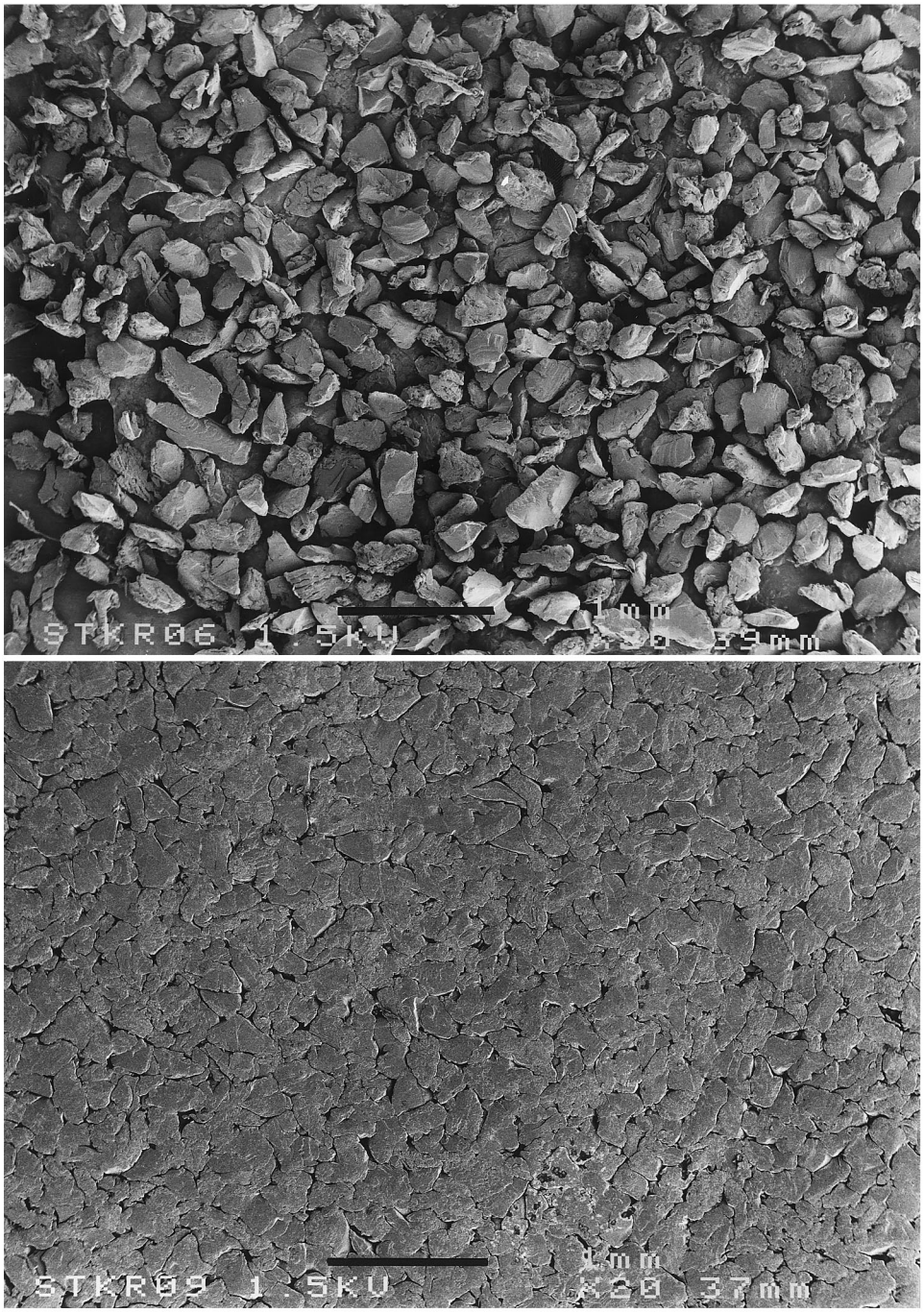

Fig. 1. SEM photographs of (a) loose PDLA powder ($d_{50} = 215$ μm) before compaction, (b) the tablet surface after compaction at 190 MPa ($\epsilon = 0.06$) and (c) the tablet surface after immersion in dissolution medium (37°C) for 24 h and subsequently drying. The bar represents 1 mm (original magnification 20 ×).

(c)

Fig. 1. (*Continued*)

joined together, the individual particles can still be easily distinguished, pointing to the non-occurrence of fragmentation.

Plastic deformation of the polymer particles during compression was further studied by measuring the specific surface area (S_v) of tablets prepared at different compaction pressures. Due to the formation of bonds between particles, plastic deformation would result in a decrease of the surface area available for adsorption of nitrogen molecules. Fragmentation, on the other hand, would result in an increase of S_v (Vromans, 1987). Compared to loose powder ($S_v = 0.15$ m^2/g), the specific surface area of tablets prepared at low compaction pressures (23 and 38 MPa) was found to be considerably larger ($S_v = 0.32$–0.35 m^2/g) (Table 2). This could point to the occurrence of fragmentation. However, as S_v decreased rapidly upon further increasing of the compaction pressure, which would not have been observed for a truly fragmenting material, it was concluded that plastic deformation is the dominating mechanism of consolidation.

In order to quantify the plasticity of the material and the effect of tabletting speed on compaction behaviour and tablet properties, the Heckel equation (Heckel, 1961a,b) was used to analyse the relationship between the at pressure porosity (ϵ) of the compacts under pressure and the applied pressure (p):

$$-\ln(\epsilon) = Kp + A \quad (2)$$

In Eq. (2), A is a constant and K is the slope of the linear part of the line. The Heckel relationship

Table 2
Specific surface area (S_v) of PDLA (d_{50} 146 μm) powder and tablets prepared thereof

Compaction pressure (MPa)	S_v (m^2/g)
0	0.15
23	0.32
38	0.35
75	0.26
190	0.11

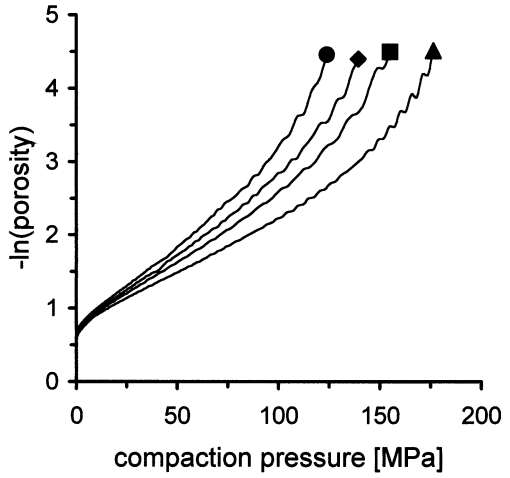

Fig. 2. Heckel plots of at pressure porosity and compaction pressure data of PDLA powder (d_{50} 146 μm) at different compaction speeds: 0.033 mm/s (●), 3 mm/s (◆), 30 mm/s (■) and 300 mm/s (▲).

was originally derived for out of die compact porosity measurements. Therefore, the reciprocal value of K is referred to as the apparent yield pressure (P_y) as it was calculated from at pressure porosity data. In Fig. 2, Heckel curves of PDLA compacted at different speeds are shown. At low pressures, densification occurred through particle rearrangement and slippage and resulted in a curved region in the plot. This region was followed by a linear part (20–75 MPa) in which yielding of the material took place and densification occurred through deformation. Table 3 presents the values of the apparent yield pressures (P_y) at different compaction speeds as obtained by linear regression from the slope of the linear part of the Heckel plots between 20 and 50 MPa. The

Table 3
Apparent yield pressure (P_y) values of PDLA (d_{50} 146 μm) for varying compaction speeds

Compaction speed (mm/s)	P_y (MPa)
0.033	44.7
0.3	47.3
3	53.9
30	59.6
300	71.8

Table 4
Values of the strain rate sensitivity (SRS) of PDLA (d_{50} 146 μm) and some other materials (Roberts and Rowe, 1985)

Material	SRS
Lactose	0.162
PDLA	0.378
Avicel PH101	0.389
Sodium chloride	0.399
Mannitol	0.464
Maize starch	0.493

values of P_y ranged from 44 to 71 MPa, which points to a ductile and easily compressible material. Apparent yield pressure values as obtained from at pressure porosity data are generally lower than yield pressures calculated from 'out of die' compact porosities since at pressure P_y values contain an elastic component of deformation (Fell and Newton, 1971). The data demonstrate an increase of P_y with increasing compaction speeds. This indicates an increased resistance to deformation due to either a decrease in the extent of plastic flow or an increase in brittle behaviour, due to the time-dependent nature of plastic flow and bond formation. At high compaction speeds not enough time will be available for the full effect of the force to be exerted (Armstrong, 1997). The strain rate sensitivity (SRS) ratio (Roberts and Rowe, 1985), which is defined as

$$\mathrm{SRS} = \frac{\sigma_c(v = 300) - \sigma_c(v = 0.033)}{\sigma_c(v = 300)} \quad (3)$$

in which σ_c, which is the apparent yield strength ($\sigma_c = (3K)^{-1}$) at compaction speeds of 0.033 and 300 mm/s, is a measure of changes in visco-elastic behaviour of the particles with rate of strain. Consequently, properties of tablets compacted from a material with a high SRS are largely affected by compaction speed. The SRS ratio of PDLA was found to be 0.378, which is comparable to that of Avicel PH101 and far smaller than the SRS ratio of mannitol or maize starch (Table 4), indicating the relatively moderate compaction speed sensitivity of PDLA.

The tablet volume after ejection is generally larger than that under pressure because of elastic relaxation of the compact (Van der Voort

Maarschalk et al., 1996). By combining the compression and decompression part of the compaction cycle, elastic and plastic work of compaction can be calculated from the different areas in the force displacement plot (Fig. 3, inset). A method to determine the plasticity is to calculate the ratio of the work used to form the compact (E_2) to the total work input ($E_2 + E_3$), in which E_3 is the elastic work (Stamm and Mathis, 1976). Fig. 3 shows the force displacement curves of PDLA compacts prepared at different pressures and a compaction speed of 0.033 mm/s. Plasticity values of PDLA, as determined from the force displacement curves of Fig. 3 ranged from 97.6% (67 MPa) to 93.7% (275 MPa). For Avicel PH101 and mannitol, plasticity values of 94.1 and 58.2 have been reported (Stamm and Mathis, 1976). The high plasticity values of PDLA indicate that a large part of the energy input is utilised in irreversible plastic deformation of the material and that elastic recovery is limited during the decompression stage of the compaction cycle.

In addition to changes in tablet volume during the decompression stage, tablet volume generally also increases after loss of contact between punch and tablet and after ejection. Therefore, for a proper estimation of the complete elastic recovery, it should be determined after complete stress relaxation of tablets. The difference between the volume of the tablet after ejection and relaxation and that under pressure is a well-known method describing tablet relaxation. Stress relaxation can be defined as the relative increase in volume after complete relaxation of the tablets after compression:

$$\Delta V = \frac{V_\infty - V_{\min}}{V_{\min}} \quad (4)$$

where V_∞ is the tablet volume at least 20 h after ejection (complete stress relaxation assumed), and $V_{\min}$ is the minimum tablet volume under pressure. Fig. 4a shows that the relative volume change of the tablets increases with both the compaction pressure and speed, the latter being the result of increasing elasticity of the material. The observed values of ΔV ranged from 10 to 23% which is smaller than the values obtained for pregelatinised potato starch (Paselli® WA4, 200 MPa $\Delta V = 19$–32%) but larger than for microcrystalline cellulose (Pharmacel® PH101, 200 MPa $\Delta V = 6$–11%) (Van der Voort Maarschalk, 1997). From the force displacement data, stress relaxation or volume increase during the decompression stage (ΔV_{comp}) can be determined with Eq. (4) if V_∞ is substituted by the tablet volume at which the punch has lost contact with the compact and the pressure has dropped to zero ($V_p = 0$). For PDLA compacts prepared at 67 and 275 MPa (0.033 mm/s), ΔV_{comp} values were 0.040 and 0.062, respectively. After relaxation for 24 h, ΔV values of 0.0883 and 0.11 were found. These results clearly show that although there is an instantaneous elastic recovery during the decompression phase, as can be deduced from the force displacement curves, a considerable part of the elastic recovery occurs after loss of contact between punch and compact in die and out of die after ejection of the tablet.

Fig. 4b presents the porosity of the tablets after ejection and relaxation. The curves show that the porosity reaches a limiting value, which is affected by the compaction speed. The minimum attainable porosity at a compaction speed of 300 mm/s was approximately 0.13.

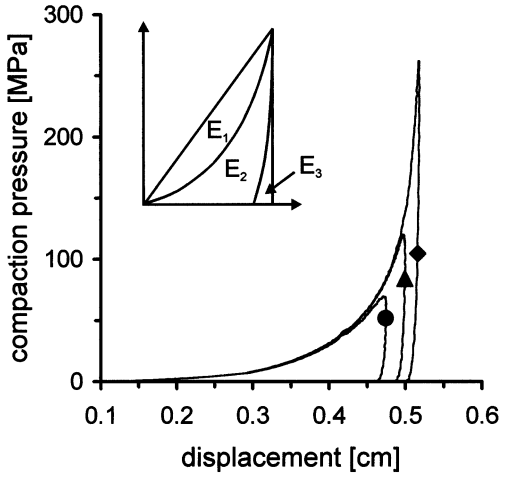

Fig. 3. Force-displacement curves of compression of PDLA at a compaction speed of 0.033 mm/s. Compaction pressures were: 70 MPa (●), 120 MPa (▲), 260 MPa (◆). The inset shows the different areas of the force-displacement curve from which the elastic (E_3) and plastic work (E_2) of compression were calculated.

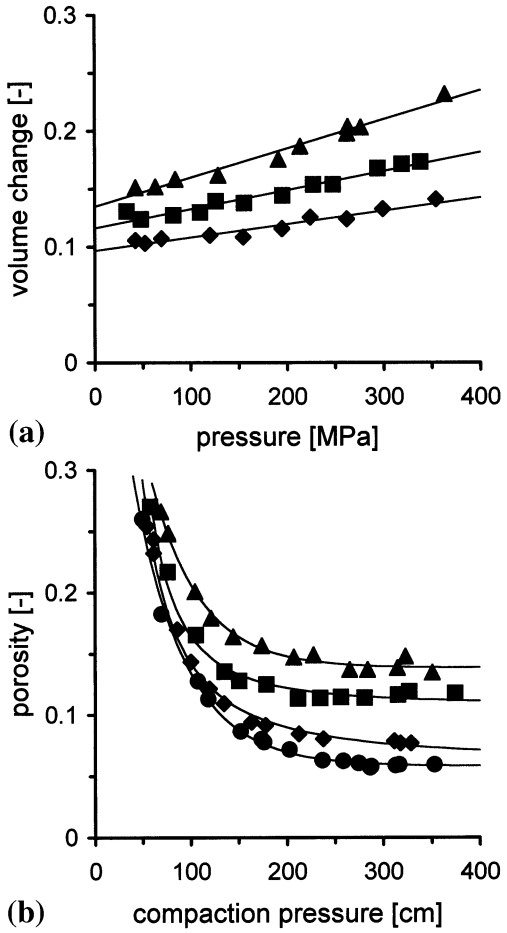

Fig. 4. Volume change of the tablets (a) and porosity of the prepared tablets after compaction and relaxation for 20 h (b) as a function of compaction pressure at different tabletting speeds: 0.033 mm/s (●), 3 mm/s (◆), 30 mm/s (■) and 300 mm/s (▲).

Generally, a clear correlation between compaction pressure and mechanical strength of tablets is observed. A proper mechanical strength is an essential property with respect to packing, transportation, storing, as well as administration of tablets. Fig. 5 depicts the relation between tensile strength of the tablets and applied compaction pressure. Despite the low specific surface area of the powder (0.15 m^2/g) even at high compaction speed tablets with good mechanical properties could be prepared ($v = 300$ mm/s, tensile strength ≈ 2.5 MPa). This is obviously caused

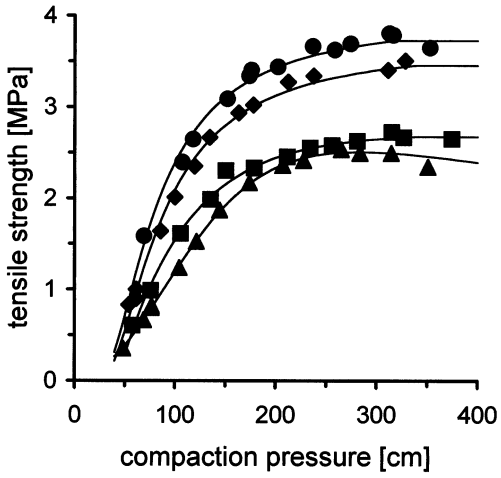

Fig. 5. Tensile strength of PDLA tablets as a function of compaction pressure at different compaction speeds: 0.033 mm/s (●), 3 mm/s (◆), 30 mm/s (■) and 300 mm/s (▲).

by the large extent of plastic deformation of the powder. As expected, upon increasing the compaction speed, a decrease of the tensile strength was observed, due to the time-dependent nature of plastic flow and bond formation.

For Paselli® WA4 (a ductile starch excipient) tablets, the relationship between tensile strength and tablet porosity was observed to be independent of the speed of compression (Van der Voort

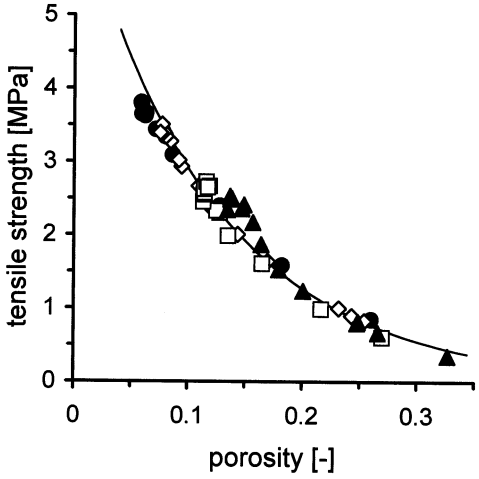

Fig. 6. Tensile strength of PDLA tablets as a function of porosity at different compaction speeds: 0.033 mm/s (●), 3 mm/s (◇), 30 mm/s (□) and 300 mm/s (▲).

Table 5
Fit parameters of Ryshkewitch–Duckworth equation to describe tensile strength–porosity relationship of PDLA (d_{50} 146 μm) compacts prepared at different compaction speeds

Compaction speed (mm/s)	k (−)	E_0 (MPa)	r^2 (−)
0.033	7.26	5.8	0.997
3	8.00	6.3	0.999
30	9.45	7.7	0.991
300	10.31	10.3	0.994

Maarschalk et al., 1996). Fig. 6 depicts the relation between the tensile strength and porosity of PDLA tablets compressed at different compaction speeds and pressures. In order to analyse the effect of compaction speed on the relation between tensile strength and porosity, the data of the different compression rates was fitted according to the Ryshkewitch–Duckworth relation (Duckworth, 1953):

$$\ln \frac{E}{E_0} = -k\epsilon \quad (5)$$

in which E is the tensile strength of the tablet, E_0 the tensile strength at zero porosity, ϵ the porosity of the tablets and k a constant, which is also called the 'bonding capacity'. High values of k point to strong bonding of particles. By means of linear regression analysis, values of k and E_0 were obtained (Table 5). The data demonstrate higher bonding capacity and higher tensile strength with increasing compaction speed. A possible explanation for this observation takes into account a rise of the temperature of the tablets when prepared at high compaction speed. Locally, at inter-particle contact points, the temperature may increase considerably. As PDLA has a relatively low glass transition temperature of approximately 50°C, increasing temperatures will facilitate the occurrence of plastic flow. Consequently, the mechanical strength of the porous compact will be enhanced. Therefore, although the minimum attainable tablet porosity increases with increasing compaction speed (Fig. 4b), even at high compaction speeds, it is possible to produce tablets with sufficient mechanical strength.

3.2. Drug release from poly(DL-lactic acid) tablets

Upon immersion of the tablets into dissolution medium, it was observed that the tablet volume largely increased without forming a gel layer. The cylindrical geometry of the tablets did not change even after several weeks of immersion. No erosion occurred as was concluded from weighing the immersed tablets after drying to constant weight.

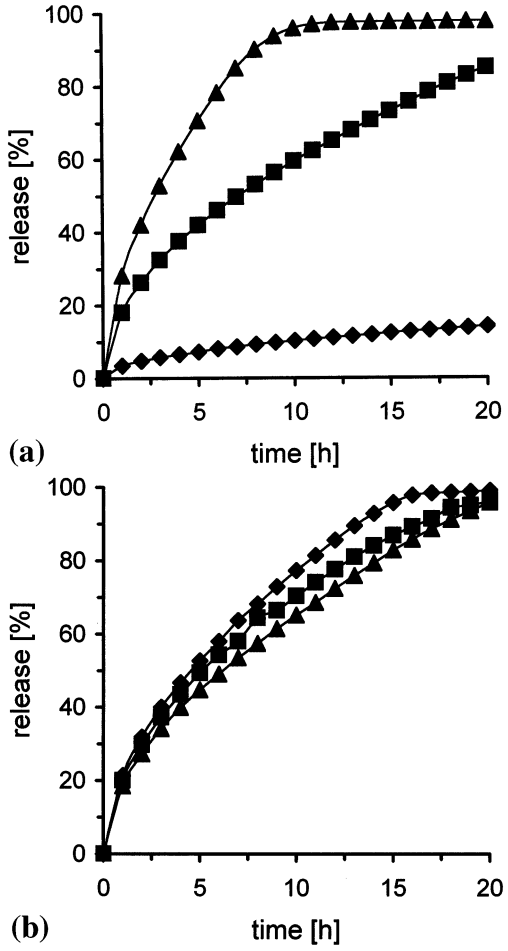

Fig. 7. Release of (a) paracetamol (▲), theophylline (■) and prednisolone (◆) from PDLA tablets (500 mg tablets containing 200 mg drug) and (b) effect of initial porosity on release of theophylline from PDLA tablets with varying initial porosities: $\epsilon = 0.14$ (◆), 0.10 (■), 0.06 (▲) (500 mg tablets containing 100 mg drug).

The release profiles of illustrative drugs with different solubilities are shown in Fig. 7a. The release of all drugs was significantly sustained indicating the suitability of PDLA as a controlled release excipient. The dissolution rate increased with the aqueous solubility (C_s) of the compounds (paracetamol $C_s = 15$ g/l, theophylline $C_s = 8.3$ g/l and prednisolone $C_s = 0.2$ g/l at 20°C) pointing to a diffusion-controlled release system. It was found that dissolution of the incorporated drugs obeyed first order kinetics during the total release time. Generally, for diffusion-controlled systems, after 60–70% of the drug is released, release no longer obeys the first order kinetics due to exhaustion of the matrix. The next section describes the influence of varying factors such as initial porosity and drug load on the dissolution kinetics. Theophylline was chosen as the model drug.

Compaction experiments already showed the effect of tabletting speed and pressure on the final porosity of the tablets (Fig. 4b). Generally, due to the leaching-type release mechanism, drug release from non-swellable tablets is highly affected by the initial porosity of the tablet (Higuchi, 1963). Fig. 7b shows the release of theophylline from PDLA tablets with initial porosities ranging from 0.06 to 0.14. The curves clearly show that the initial porosity only slightly affected the release rate. After 16 h of immersion in the dissolution medium, 80–100% of the drug was released, irrespective of the initial porosity. The reason for the lack of effect of the initial porosity is the rapid and large volume expansion of the tablets, which resulted in the formation of a large pore fraction shortly after immersion of the tablets. After 2 h of immersion, all tablets, irrespective of their initial porosity, had a pore fraction ranging from 0.35 to 0.43. In addition, it was observed that the addition of 0.5% w/w magnesium stearate as a lubricant and pH of the dissolution medium (not shown) did not have any affect on the release. The pH insensitivity of high molecular weight PDLA is in high contrast to that of low molecular weight PDLA (Moll and Köller, 1990).

The effect of drug load on the release of theophylline from PDLA tablets is shown in Fig. 8. For drug loads ranging from 0.20 to 0.60, the drug was released according to a first order release profile. Lower and higher drug loads, however, resulted in nearly linear release profiles. In contradiction to what is generally observed, release slowed down upon increasing the drug load from 0.04 to 0.20. Generally, release of low-dosed drugs from tablets without an additional soluble excipient is slow and incomplete as a considerable amount of the incorporated drug is trapped in the matrix. Our results show the suitability of PDLA as a release controlling excipient in matrix tablets for the administration of low dosed drugs. For drug loads exceeding 0.50, faster drug release was observed as would be expected for matrix-type tablets. Due to dissolution of drug particles, the carcass porosity increases and the occurrence of erosion and disintegration of the tablets is facilitated, especially at higher drug loads. Indeed, for drug loads exceeding 0.60, erosion was observed. Further increasing of the drug load resulted in disintegration of the tablets. These effects are more clearly illustrated by plotting the fractional release rate constant B versus the drug load (Fig. 9). B was determined according to:

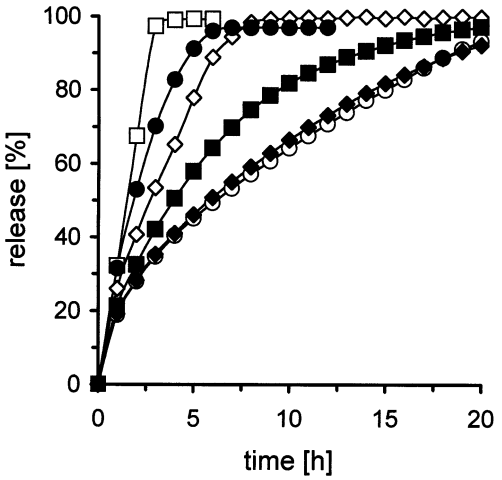

Fig. 8. Release of theophylline from PDLA tablets (500 mg tablets) containing different drug loads: 20 mg (□), 50 mg (◇), 100 mg (○), 250 mg (◆), 300 mg (■), 400 mg (●).

$$\frac{M_t}{M_0} = B\sqrt{t} \tag{6}$$

in which M_t/M_0 is the fraction released after a specific period. Below a drug load of 0.20, B

steeply decreased with increasing drug load. For drug loads between 0.20 and 0.50, B was found to be nearly constant implicating that in this range the fractional drug release from the PDLA compacts is independent of the drug load. For drug loads exceeding 0.50, B was found to increase steeply with drug load due to erosion and disintegration of the tablet. For comparison, the fractional release rate constant for the release of theophylline from tablets prepared with Ethocel® 7 cPs, an inert matrix tablet excipient, is also shown. The fractional release rate constant of the theophylline/ethyl cellulose tablets steadily increased with increasing drug load as would be expected for a leaching-type release mechanism.

The remarkable effect of the drug load on the release rate constant can be explained by taking into account the expansion behaviour of PDLA tablets. The SEM photograph of Fig. 1c shows the surface morphology of a tablet of 100% PDLA after 24 h of immersion. The PDLA particles in the tablet regain their pre-compaction shape during immersion in water, which results in volume expansion of the tablets. Consequently, a large pore fraction is formed which is rapidly filled with water. Upon decreasing the PDLA fraction of the tablets, the pore volume originating from the recovery of the pre-compaction shape of PDLA particles, decreases. However, as the drug fraction increases, additional pore volume is created due to dissolution of drug particles. Combination of volume expansion and release data enabled us to calculate the total pore volume of the tablets during immersion. The total pore volume of tablets with different drug loads after 2 h of immersion is shown in Fig. 10. It can be clearly seen that the total pore volume decreases steadily upon increasing the drug load from 0.04 to 0.50. When we calculate the pore volume per drug weight, the effect is even more pronounced. The pore volume per drug weight decreases sharply for drug loads between 0.04 and 0.20 theophylline and, subsequently, levels off to a plateau value. This relationship is similar to and explains the steep decrease of B in the lower drug load range and the plateau value of B for theophylline fractions between 0.20 and 0.50 in Fig. 9. Above a drug load of 0.50, the total pore volume mainly originates from dissolution of drug particles. Therefore, although the pore volume per drug weight has reached its plateau value, the total pore volume increases steeply due to dissolution of the drug. As the polymeric phase does not form a percolating matrix at high drug loads,

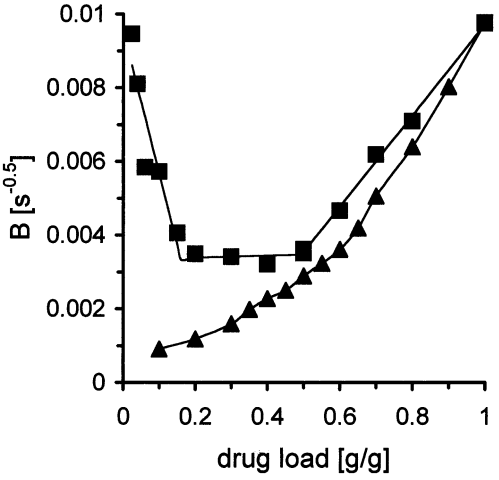

Fig. 9. Release rate constant B of theophylline, as calculated according to Eq. (6), as a function of the drug load (expressed as theophylline weight per tablet weight) of PDLA (■) and Ethocel® 7 cPs (▲) tablets.

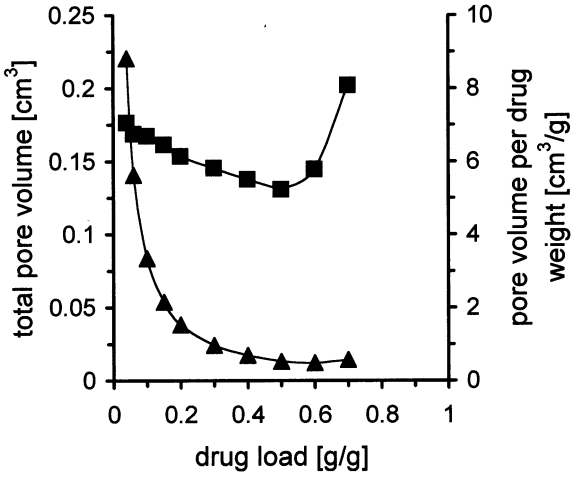

Fig. 10. Total pore volume (■) and pore volume per drug weight (▲) of PDLA/theophylline tablets as a function of drug load (expressed as theophylline weight per tablet weight) after 2 h of immersion.

disintegration of the tablet and rapid release of the drug occurs.

4. Conclusion

High molecular weight poly(DL-lactic acid) proved to be a suitable excipient for the preparation of controlled release tablets by direct compression. Tabletting experiments demonstrated the very ductile character and the moderate strain rate sensitivity of the polymer. Even at high compaction speed, tablets having satisfying mechanical properties could be prepared. A variety of drugs ranging in aqueous solubility from prednisolone to paracetamol, demonstrated first order release from PDLA tablets, unaffected by pH and lubrication and only slightly affected by the initial porosity of the tablet. From the surprising relationship between the drug load and fractional release rate it was concluded that PDLA has unique and promising properties as a direct compression and release controlling excipient in matrix tablets for the oral administration of low dosed drugs. It was concluded that the remarkable drug release properties originate from the volume expansion of the PDLA tablets.

Acknowledgements

The authors would like to thank A.C. Eissens for his assistance with the compaction experiments. They are also grateful to H.W. Frijlink for helpful suggestions regarding the compaction experiments. Hycail (Noordhorn, The Netherlands) is acknowledged for kindly supplying poly(DL-lactic acid).

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