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Research Article

Sugar End-Capped Poly-D,L-lactides as Excipients in Oral Sustained Release Tablets

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Abstract. Sugar end-capped poly-D,L-lactide (SPDLA) polymers were investigated as a potential release controlling excipient in oral sustained release matrix tablets. The SPDLA polymers were obtained by a catalytic ring-opening polymerization technique using methyl α-D-gluco-pyranoside as a multifunctional initiator in the polymerization. Polymers of different molecular weights were synthesized by varying molar ratios of monomer/catalyst. The matrix tablets were prepared by direct compression technique from the binary mixtures of SPDLA and microcrystalline cellulose, and theophylline was used as a model drug. The tablet matrices showed *in vitro* reproducible drug release profiles with a zero-order or diffusion-based kinetic depending on the SPDLA polymer grade used. Further release from the tablet matrices was dependent on the molecular weight of the SPDLA polymer applied. The drug release was the fastest with the lowest molecular weight SPDLA grade, and the drug release followed zero-order rate. With the higher molecular weight SPDLAs, more prolonged dissolution profiles for the matrix tablets (up to 8–10 h) were obtained. Furthermore, the prolonged drug release was independent of the pH of the dissolution media. In conclusion, SPDLAs are a novel type of drug carrier polymers applicable in oral controlled drug delivery systems.

KEY WORDS: direct compression; matrix tablets; poly-D,L-lactide; release kinetics; sustained release; theophylline.

INTRODUCTION

Only very few new excipients aimed for controlling oral drug release have come on the markets during the last 20 years, although there is an increasing need to be able to modify accurately drug release profile and kinetics for various types of drug substances. The main material groups used in drug release control from oral matrices have been cellulose derivatives, starches, polyethylene glycols, ionic exchangers, and methacrylates (1–4). Particularly, there is a need for an excipient group by which drug release rate can be modified in a wide range.

Poly(D,L-lactide) (PDLA) is an amorphous, biodegradable, and aliphatic polyester polymer. Low molecular weight PDLAs can be directly prepared from lactic acid, but the most efficient way to produce high molecular weight polymers in a controllable manner is by catalyst-assisted, ring-opening polymerization (ROP) of six-membered cyclic diesters (5). Molecular weight can greatly affect chemical and physical–mechanical properties such as degradation, solubility, viscosity, diffusivity, and glass transition temperature (6).

Direct compression tablets based on PDLA and a drug have delivered the drug according to profiles suitable either for implantable (7–10) or for oral dosage forms (11–14). In literature, however, the results on suitability of low molecular weight PDLAs for oral drug delivery tablets have been contradictory. For example, low molecular weight PDLA (M_W 6,000) exhibited good compaction (15) and sustained release controlling properties in matrix tablets (11). However, since drug release from tablets containing low molecular weight PDLA (M_W 2,000) was highly pH-dependent (12), it was concluded that low molecular weight PDLA might not be suitable for peroral application.

By using higher molecular weight PDLAs, limitations caused by pH dependence can be avoided. One series of studies with high molecular weight PDLA (M_v 85,000) as a release controlling excipient in matrix tablets prepared by direct compression have been performed by Steendam and Lerk (13). However, a high molecular weight causes difficulties in mechanical grinding in order to get the polymer granules into a powder form. Further, Steendam *et al.* (14) reported that sustained drug release was only slightly affected by molecular weight.

Surprisingly, only two reports about combining PDLA and other tablet excipient for oral drug delivery application have been published so far. Omelczuk and McGinity (16,17)

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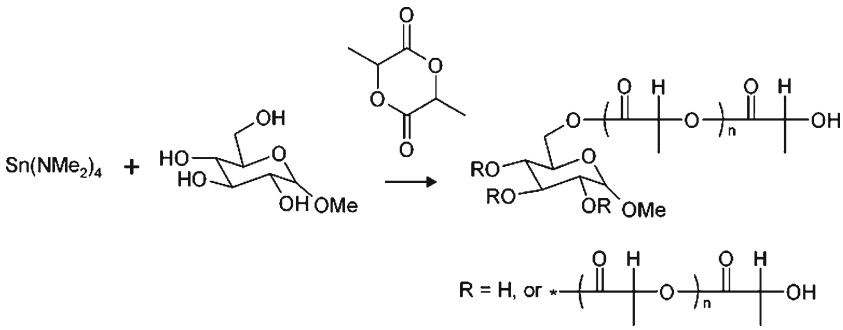

Fig. 1. Schematic presentation of $Sn(NMe_2)_4$ catalyzed ring-opening polymerization of D, L-lactide in the presence of methyl α-D-glucopyranoside. Polymerizations conducted in toluene at 120°C for 17 h (initial monomer concentration $[M]^0$=1.0 M)

applied a wet granulation method for the mixing of PDLA and microcrystalline cellulose (MCC) or lactose for tablet preparation. The influence of molecular weight as well as thermal treatment on the drug release from PDLA/MCC or PDLA/lactose sustained release matrix tablets was studied. The release of the drug slowed down progressively as the molecular weight increased (16).

The main aim of this study was to evaluate the properties of sugar end-capped poly (D,L-lactides) (SPDLAs) as a novel excipient group for pharmaceutical sustained release applications. The strong hypothesis is that drug release rate can be modified in a wide range by using SPDLAs with different molecular weights and water solubilities. The sustained release matrix tablets were prepared by direct compression technique from the binary mixtures of SPDLAs and MCC.

MATERIALS AND METHODS

Materials

Monomer, D,L-lactide was purchased from PURAC biochem (Purasorb DL) and was recrystallized from toluene. Microcrystalline cellulose, MCC (Avicel PH 102, FMC International, Cork, Ireland) was used as a direct compression co-filler for SPDLAs. Theophylline anhydrate (Ph.Eur.) was chosen as a model drug because its solubility in the acidic and neutral dissolution media is known to be similar (8). Magnesium stearate (Ph.Eur.) was used as a lubricant.

Analytical Methods

Nuclear Magnetic Resonance Studies

^1H (300 Hz) nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury 300 spectrometer at 27°C in $CDCl_3$. Chemical shifts are expressed as parts per million. The ^1H spectra are referenced relative to $CHCl_3$ (7.27 ppm).

Gel Permeation Chromatography

Molecular weights and molecular weight distributions were measured at 35°C in tetrahydrofuran by size exclusion gel permeation chromatography (GPC) relative to polystyrene standards with a Waters 515 HPLC pump; GPC fitted with Styragel columns HR 1, HR 2, and HR 4; a UV detector-Waters 2487; and a refractive-index detector-Waters 2410.

Differential Scanning Calorimetry

The glass transition temperatures (T_g) of polymers were determined with a Mettler 822e differential scanning calorimetry (DSC) under nitrogen. The measuring temperature range was from −30°C to +100°C. The samples of about 5 mg in simply sealed aluminum pans were first heated from +25°C to +100°C to destroy the thermal history and then cooled to −30°C and heated again to +100°C. Heating rate was 15°C/min and cooling rate was 30°C/min (holding time was 5 min).

Fourier Transform Infrared Spectroscopy

The Fourier transform infrared spectroscopy (FTIR) spectra (Perkin-Elmer Spectrum GX spetrometer) of the polymers were obtained from potassium bromide disks (200 mg, 3% polymer) compressed with hydraulic press. The KBr tablet disk was placed into the IR sample holder and measured with 64 scans from 4,000 to 370 cm^{-1} with 0.5 cm^{-1} nominal resolution.

Polymerization of SPDLAs and Preparation of SPDLA Powder

In the polymerization of SPDLA polymers (Fig. 1), $Sn(NMe_2)_4$ was applied as a catalyst precursor for the ROP of D, L-lactide and the reaction was initiated with hydroxyl groups on methyl α-D-glucopyranoside. Three SPDLA batches of different molecular weights were obtained depending on molar ratios of monomer/initiator ([M]/[I]) used for polymerization (Table I).

The obtained mixture of monomer and polymer was analyzed by ^1H NMR to determine conversion. The polymer was purified from the monomer by precipitation from

Table I. Conversions Determined by ^1H NMR and Molecular Weights (M_w and M_n) Analyzed with GPC for Three Sugar End-Capped Poly-D,L-lactide (SPDLA) Polymer Batches

SPDLA batch	[Monomer]/[initiator]	Conversion (%)	M_w (g/mol)	M_n (g/mol)
SPDLA_5300	25/1	96	5,300	4,400
SPDLA_11000	50/1	95	11,000	8,700
SPDLA_17000	100/1	87	17,000	13,000

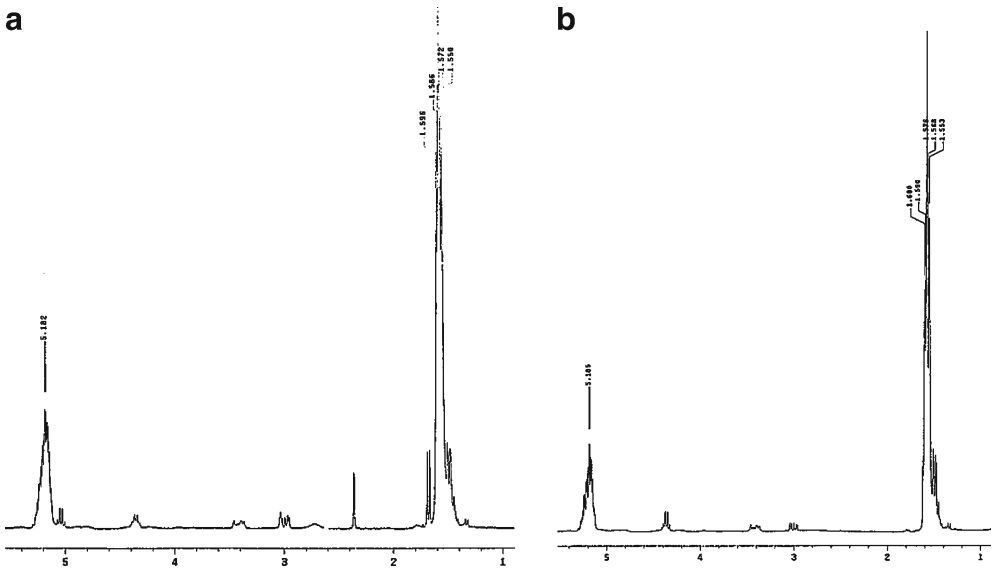

Fig. 2. ^{1}H NMR spectrum of sugar end-capped poly-D,L-lactide (SPDLA) polymer (M_w=5300) **a** before and **b** after removal of residual monomer

dichloromethane/hexane solution (1:3) and analyzed with GPC and DSC to determine molecular weight and glass transition temperature. By evaporating solvents using a vacuum pump, a polymer foam was obtained. This foam was gently crushed in a mortar to grind it into a free-flowing powder. For convenience, the polymers will be referred to in the following discussion by the designation SPDLA_M_w, *i.e.*, an SPDLA_5300 polymer is a polymer with a molecular weight of 5,300.

Preparation of Sustained Release Matrix Tablet

The composition of the powder mixture for direct compression of the tablet matrices was as follows: 46.75%

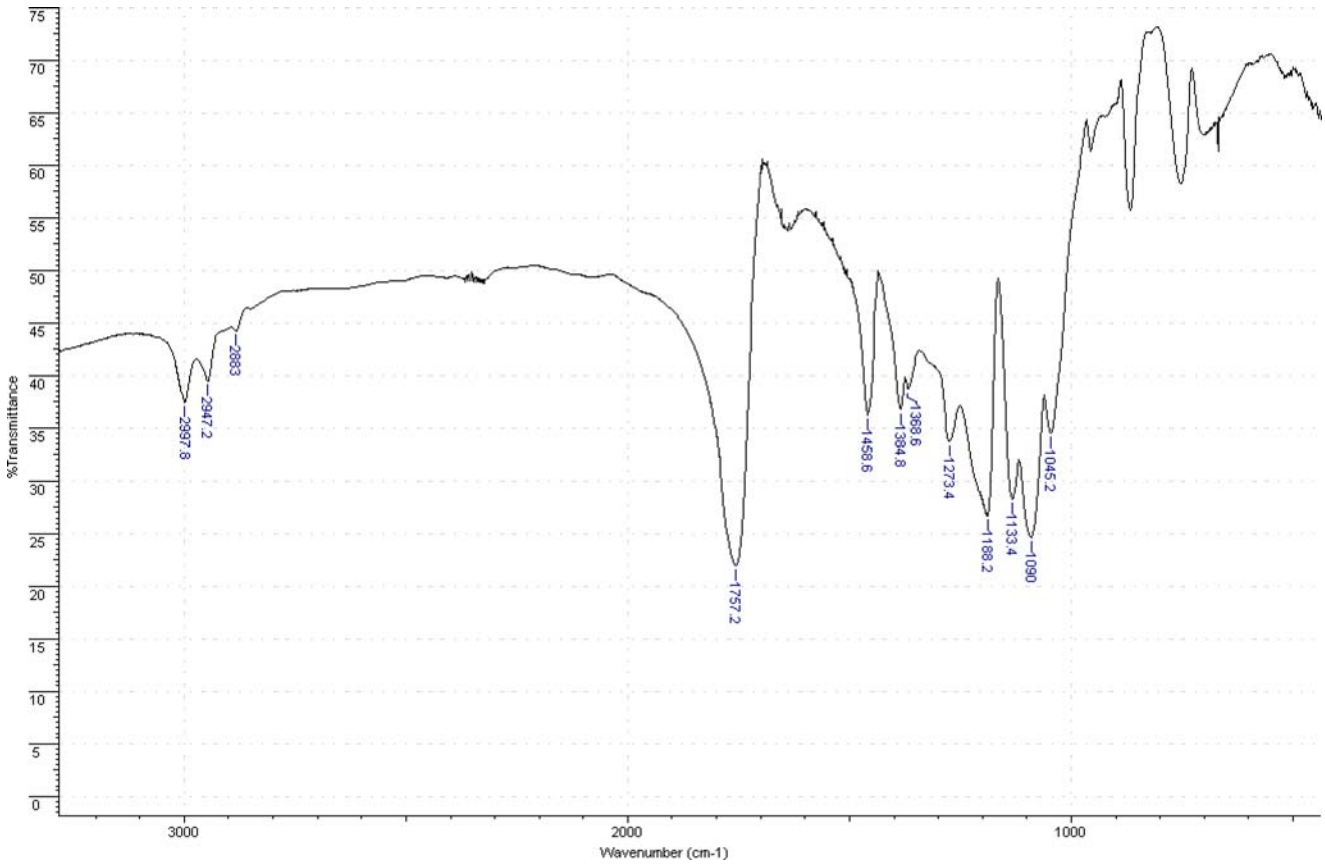

Fig. 3. Fourier transform infrared spectrum of sugar end-capped poly-D,L-lactide (SPDLA) polymer (M_w=5,300) in the region 3,300 to 500 cm^{-1}

Table II. Peak Assignment for Sugar End-Capped Poly-D,L-lactide (SPDLA) Polymer (M_w=5,300) Fourier Transform Infrared Spectrum

Assignment	Peak center (cm^{-1})
–CH-stretch	2,997.8; 2,947.2
–C=O carbonyl stretch	1,757.2
$–CH_3$ bend	1,458.6
–CH-deformation	1,384.8; 1,368.6
–C=O bend	1,273.4
–C–O-stretch	1,188.2; 1,133.4; 1,090
–OH-bend	1,045.2

SPDLA, 46.75% MCC, and 6% theophylline with 0.5% magnesium stearate acting as a lubricant. Physical mixtures were prepared by mixing the components in a Turbula mixer (W.A. Bachofen, Switzerland) at 32 rpm during 20 min. After the addition of magnesium stearate, mixing was continued for three subsequent minutes.

Cylindrically flat-faced tablets (250 mg, diameter 9 mm) were manually compressed using an instrumented single-punch tablet machine (Korsch EK-0, Erweka Apparatebau GmbH, Germany). To separate the constituent effects from hardness effects, tablets of each SPDLA grade were compressed to a constant hardness of 90 N by varying the mass of powder mixture for different SPDLA grades.

Study of the Tablet Surface by Scanning Electron Microscopy

Scanning electron micrographs (SEMs) were taken before and after the dissolution test to estimate the tablet surface structure and alterations caused by dissolution. The micrographs were taken with a Zeiss DSM-962 (Carl Zeiss, Oberkochen, Germany) scanning electron microscope. Before scanning, the samples were coated with platinum using a vacuum evaporator. SEM images were obtained at an accelerated voltage of 8 to 10 kV.

Dissolution Studies

The *in vitro* release tests were performed using an USP test apparatus type 1 (basket apparatus). The dissolution media were 0.2 M phosphate buffer (pH 6.8), 0.05 M acetate buffer (pH 4.5), and 0.1 M hydrochloric acid (pH 1.0) maintained at 37±0.5°C. The basket rotation speed was kept at 50 rpm and the amount of dissolution media was 900 ml. During the dissolution test, samples were withdrawn from the dissolution medium at certain times and replaced with the same volume of fresh dissolution medium. The concentration of theophylline in each sample taken was analyzed using an ultraviolet (UV) spectrophotometer (LKB Ultraspec® II). The analytical wavelength was 270 nm in 0.1 N hydrochloric acid, 271 nm in pH 4.5 acetate buffer, and 272 nm in pH 6.8 phosphate buffer.

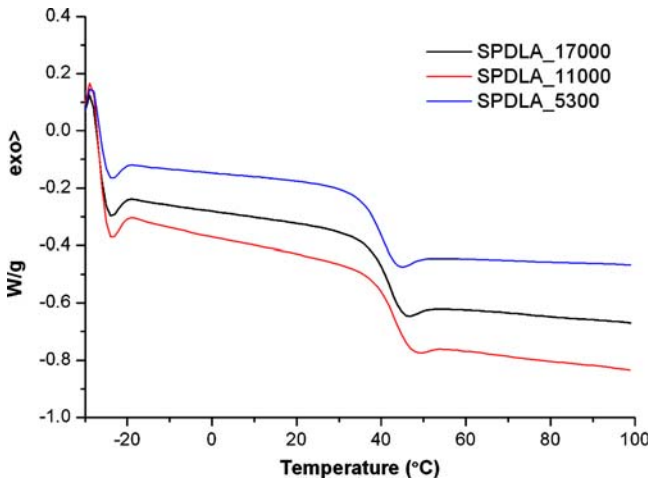

Fig. 4. Differential scanning calorimetry data of sugar end-capped poly-D,L-lactide (SPDLA) polymers

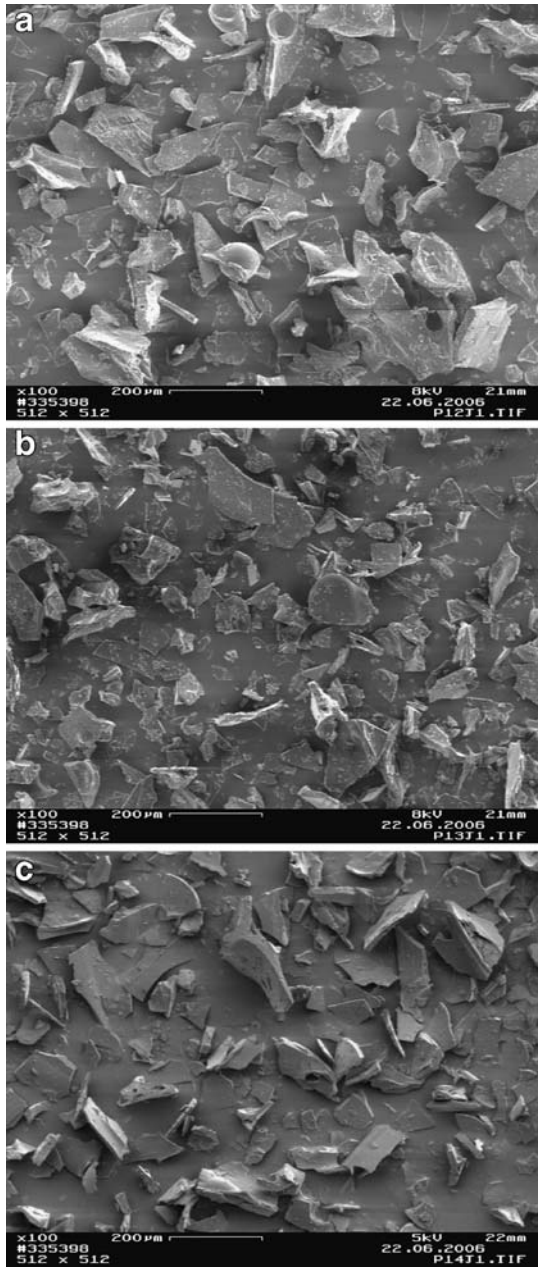

Fig. 5. Scanning electron micrographs (SEM) of sugar end-capped poly-D,L-lactide (SPDLA) polymers in powder form. Key: **a** a SPDLA_5300 polymer, **b** SPDLA_11000 polymer, and **c** a SPDLA_17000 polymer. Magnification ×100

RESULTS AND DISCUSSION

The series of three SPDLA polymers with different molecular weights were prepared for direct compressed controlled release tablets. For the synthesis of SPDLAs, Sn $(NMe_2)_4$ was applied as a catalyst precursor and was prepared according to a literature procedure (18). A Sn-amido bond is susceptible for the hydrolysis, and as depicted in Fig. 1, a treatment with an alcohol (here methyl α-D-glucopyranoside) selectively generates the corresponding tin alkoxide complex. In comparison with other published tin-based catalyst precursors, Sn(IV)alkoxides and Sn(II)octoate, this is the marked benefit of $Sn(NMe_2)_4$. Due to the generated tin–oxygen bond, the tin alkoxide complex is the actual catalyst for the ROP. In the polymer, the initial alkoxide moiety appears as a chain end group (19).

Applied tin initiator is active toward polymerization of D, L-lactide in toluene at 120°C and gives high conversion (96%, 95%, and 87%) after 17 h. Monomer conversion was determined by integrating the relative intensities of the methyl resonances attributable to the monomer and polymer. The ^{1}H-NMR of SPDLA_5300 (Fig. 2a) shows the peaks at 1.68 (doublet) and 1.5 ppm, which are assigned to methyl protons in the monomer unit and in the polymer. The complete removal of monomer by precipitation from CH_2Cl_2/hexane solution was verified by ^{1}H NMR (Fig. 2b).

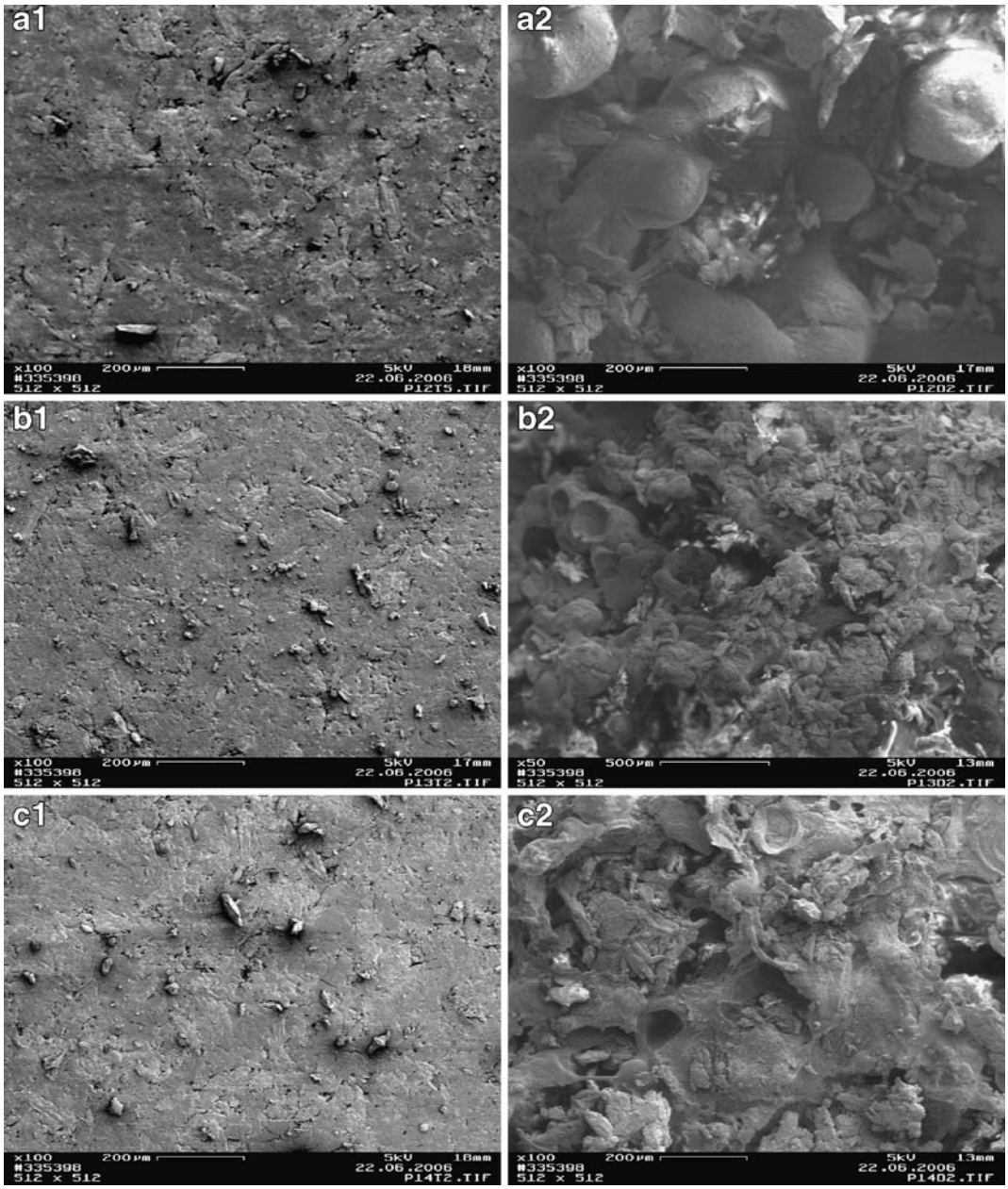

Fig. 6. Scanning electron micrographs (SEM) on the surface of initial sustained release sugar end-capped poly-D,L-lactide (SPDLA) matrix tablet before and after exposition to the dissolution test at pH 6.8. Key: *a1–2* a SPDLA_5300 polymer, *b1–2* a SPDLA_11000 polymer, and *c1–2* a SPDLA_17000 polymer. Magnification ×100

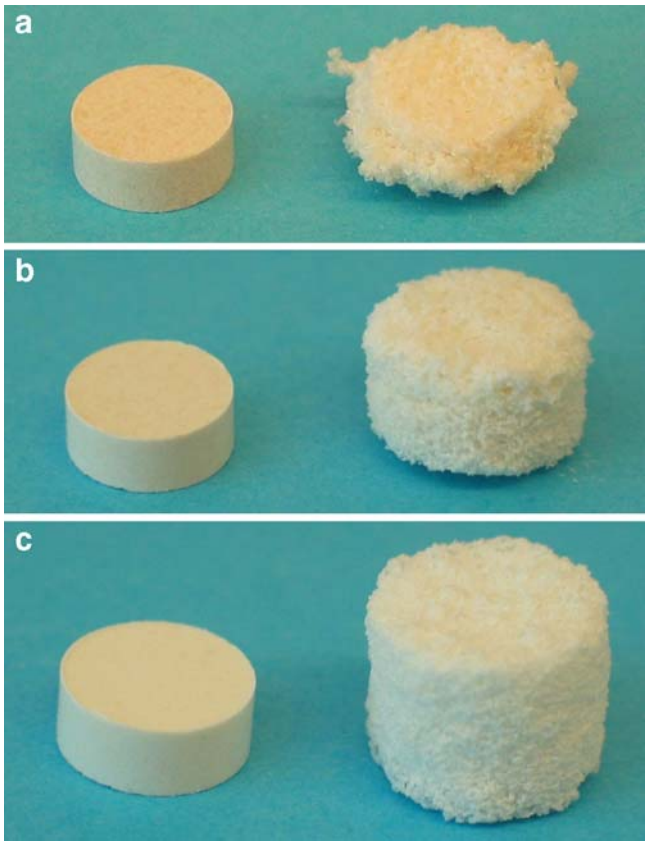

Fig. 7. Stereomicroscopic photographs of sustained release sugar end-capped poly-D,L-lactide (SPDLA) matrix tablets before and after exposition to the dissolution test at pH 6.8. Key: **a** a SPDLA_5300 polymer, **b** a SPDLA_11000 polymer, and **c** a SPDLA_17000 polymer

The molecular weight of the polymers can be controlled with high precision due to the living nature of the polymerization reaction. For this study, a series of three sugar end-capped polymers with molecular weights of 5,300, 11,000, and 17,000 g/mol were selected for future studies. After purification, the polymers were dissolved into CH_2Cl_2, and subsequent removal of the solvent with vacuum pump produced a brittle polymer foam. This turned out to be a beneficial pretreatment method for the polylactides as gentle crushing of the foam in a mortar gave fine and free-flowing polymer powder.

Characterization of SPDLAs

FTIR spectrum of SPDLA_5300 polymer is shown in Fig. 3. The assigned peaks for spectrum are listed in Table II and are congruent with the frequencies previously reported in literature for polylactides (20,21,22). FTIR spectra of SPDLA_11000 and SPDLA_17000 polymers were similar to that of SPDLA_5300 (not shown).

In order to characterize the physical state of SPDLAs, DSC analysis was performed. SPDLAs are amorphous and T_gs could be clearly detected at 39°C, 43°C, and 41°C. The differences in T_g were not significant as the molecular weight increased from 5,300 to 17,000. The glass transition temperatures of all SPDLAs were above the dissolution temperature (37°C; Fig. 4).

Powder Properties and Tableting

For preparing direct compression-sustained release matrix tablets, the release rate controlling polymer should

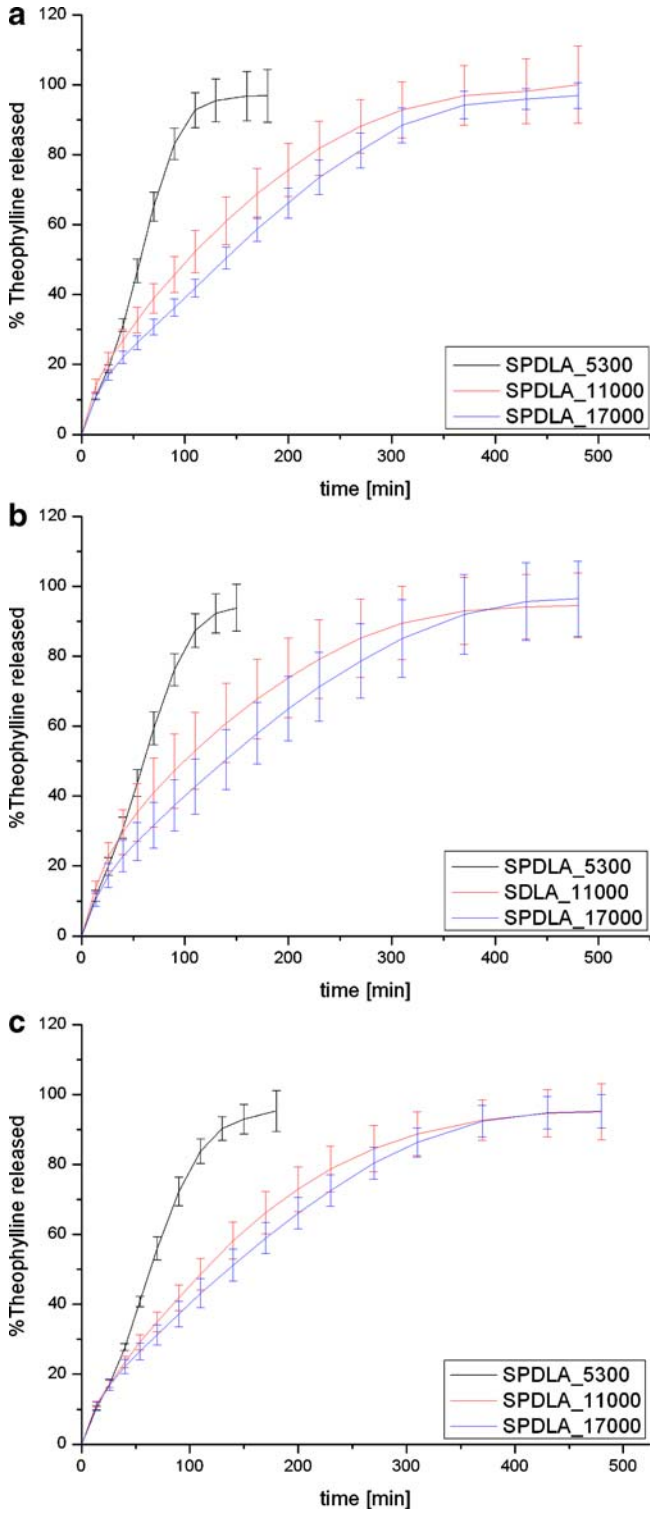

Fig. 8. Percentage of theophylline released from the compressed sugar end-capped poly-D,L-lactide (SPDLA) tablet matrices containing SPDLA_5300 polymer, SPDLA_11000 polymer, or SPDLA_17000 polymer. The dissolution tests of the tablet matrices are performed at **a** pH 1.0, **b** 4.5, and **c** 6.8

exhibit good flowing, consolidation, and compaction properties. The SEM photographs in Fig. 5 show different grade SPDLA powders which were prepared as described in the experimental section. The shape of the particles is irregular and particle size varies from 10 to 200 μm for all SPDLA grades. It was advantageous that SPDLA polymers were directly synthesized to a free-flowing and readily compressible powder form so that additional grinding stages could be avoided. According to the literature, formulation of direct compression-sustained release matrix tablets based on PDLAs has failed so far due to the fact that mechanical grinding of the present polymers is not possible (13).

From a technological point of view, no difficulties or limitations were met related to matrix tablet compression procedure. According to SEM photographs, the tablets are homogenous and form a firm matrix, with a surface free from any clearly visible particulate borderlines (Fig. 6). Comparison of Fig. 5 with Fig. 6 shows the plastic deformation of the particles as a result of compression. Further, the hardness of the tablets was high enough to resist handling and potential subsequent processing such as packaging.

Drug Release

Stereomicroscopic photographs (Fig. 7) illustrate the initial sustained release tablet matrices and the residues after the dissolution test. Upon immersion of the tablets into the dissolution medium, it was observed that the tablet volume largely increased without forming a gel layer. The swelling of the tablets also increased as the molecular weight of SPDLA increased. However, the swelling in these formulations could be mainly attributed to the MCC which has a propensity to swell. During the dissolution tests, no erosion occurred (visual inspection) and tablets did not disintegrate. Instead, reference tablets prepared using MCC alone as the matrix former disintegrated immediately.

Figure 8a–c shows the dissolution profiles of tablet matrices tested at three different pHs of the dissolution media (pH 1.0, pH 4.5, and pH 6.8). The dissolution profiles suggest that pH changes do not influence any of these preparations. pH independency is an important property because sustained release preparations should not be affected by pH changes in the digestive tract (23). The drug release was the fastest with the lowest molecular weight SPDLA grade and all of the drug load was released within approximately 2 h. These tablets were the only ones for which the drug release followed zero-order rate. A linear release profile as a function of time during the first 90 min was obtained.

As the dissolution profiles in Fig. 8a–c indicate, the tablet matrices containing 50% SPDLA_11000 exhibited clearly prolonged drug release in three different pH media. The drug release was complete after 5 h of immersion of the tablet matrices in the dissolution medium. For these tablets, a linear release relationship was obtained up to 80% when the percentage released was plotted *versus* the square root of time. This means that the release profile followed the diffusion-based kinetics. Variation in the dissolution results of individual tablets was higher compared to that obtained with the respective matrices based on the lower molecular weight SPDLA (SPDLA_5300). As expected, the tablet matrices containing 50% SPDLA_17000 exhibited prolonged drug release, and 100% of the drug load was released at 8 h after the start of the dissolution test (Fig. 8a–c). For these tablets, the drug release up to 80% exhibited a square root of time dependency.

CONCLUSIONS

Sustained release tablets were successfully prepared by a simple direct compression technique from a mixture of SPDLA polymer and MCC. Dissolution studies showed significant correlations between the properties of the SPDLA and the release profiles of the tablets. The release of theophylline slowed down progressively as the molecular weight of the SPDLA increased. The preparations were not influenced by pH in a dissolution test, suggesting that they are pH-independent. Finally, release profile of different kinds of drugs incorporated into these matrices can be modified specifically by choice of a particular polymer grade (M_w) and the proportions of SPDLA and MCC in the mixture.

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