European Journal of Pharmaceutics and Biopharmaceutics 79 (2011) 584–591

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Solutions as solutions – Synthesis and use of a liquid polyester excipient to dissolve lipophilic drugs and formulate sustained-release parenterals

Lutz R. Asmus, Robert Gurny, Michael Möller *

School of Pharmaceutical Sciences, University of Geneva & University of Lausanne, Geneva, Switzerland

ARTICLE INFO

Article history:
Received 15 February 2011
Accepted in revised form 19 July 2011
Available online 26 July 2011

Keywords:
Green chemistry
Lipophilic drugs
Sustained release
Pharmaceutical excipients
Polycondensation
Polyesters

ABSTRACT

Solid poly(lactides) and poly(lactide-*co*-glycolides) are widely used polymers for sustained-release parenterals. However, they have some unfavorable properties regarding manufacturing of the formulations and administration to the patient due to their solid aggregate state. In contrast, hexyl-substituted poly(lactic acid) (hexPLA, poly(2-hydroxyoctanoic acid)) is a viscous degradable polyester. To date, a two-step ring-opening polymerization was used for its synthesis. Here, we investigated a novel one-pot one-step melt polycondensation method to prepare hexPLA for biomedical applications by a simple green chemistry process. No catalyst or solely pharmaceutically acceptable catalysts and environmentally friendly purification methods without organic solvents were used. The resulting hexPLA polymers are stable under dry heat sterilization conditions. Low molecular weight hexPLAs with less than 5000 g/mol are less viscous than high molecular weight polymers. HexPLA can dissolve lipophilic active substances, with generally high incorporation capacities in low molecular weight polymers. The incorporation of solid compounds increases the viscosity and glass transition temperature, whereas the addition of small amounts of plasticizers or sparse warming significantly decreases the viscosity. Loratadine is soluble in hexPLA up to 28%. This highly concentrated Loratadine–hexPLA formulation released the active compound entirely over 14 days without initial burst in a zero order kinetic, matching the clinical requirements for such a sustained-release formulation. This demonstrates the potential of hexPLA as an excipient for injectable sustained-release formulations.

1. Introduction

Polyesters of 2-hydroxyacids are gaining greater importance in diverse application fields. In particular, the market for poly(lactic acid) (PLA) and its copolymers is growing fast because of its interesting material properties, such as biodegradability, and its synthesis from lactic acid, which itself can be obtained from natural sources [1–3]. The use of poly(lactic acid) in commodity throw-away plastic products is environmentally friendly in comparison with petrol based polymers since its ester bonds can easily be hydrolyzed and enzymatically degraded, making PLA compostable and entirely biodegradable [4]. The good biocompatibility of PLA and its degradation product, natural lactic acid, has made it a first choice material also for many applications in the medical field, e.g., in long acting pharmaceutical implants [5], degradable screws and sutures in reconstructive surgery [6,7], and drug loaded microparticles [7]. The properties of PLA, such as its glass transition temperature T_g, crystallinity, lipophilicity, and degradation time, can be changed by modifying the stereochemistry of the monomer units, the molecular weight, or by copolymerization, e.g., with biocompatible poly(glycolic acid) [5]. Although these characteristics can be adjusted over a wide range for different applications, one major problem limits the use of PLA: its solid aggregate state hampers the formulation of sensitive active substances into the polymer matrix, since heat or organic solvents are needed. Moreover, PLA injectable medications are not possible without formulating the material as micro- or nanoparticles or adding further excipients [8].

A liquid, biocompatible polyester-based polymer, which could be simply mixed with an active substance under mild conditions, would facilitate injectable formulations. This, together with the need for lipophilic excipients that are able to dissolve the more lipophilic modern drugs (more than 9 out of 10 new chemical entities (NCE) are poorly water soluble) [9], is an unmet need in the pharmaceutical field. Hexyl-substituted poly(lactic acid) (hexPLA, poly(2-hydroxyoctanoic acid)) is a novel polymer based on 2-hydroxyoctanoic acid monomer units. The methyl groups along the polymer backbone of PLA were substituted by hexyl groups resulting in a polymer with new characteristics. Its longer aliphatic side chains act as internal plasticizers, significantly reducing the T_g in comparison with PLA and hereby leading to a viscous liquid

* Corresponding author. School of Pharmaceutical Sciences, University of Geneva & University of Lausanne, Quai Ernest-Ansermet 30, 1211 Geneva, Switzerland. Tel.: +41 22 379 31 32; fax: +41 22 379 65 67.

E-mail addresses: Lutz.Asmus@unige.ch (L.R. Asmus), Robert.Gurny@unige.ch (R. Gurny), Michael.Moeller@unige.ch (M. Möller).

0939-6411/$ - see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2011.07.007

material [8,10]. Like for any new excipient, the biocompatibility of hexPLA needs to be evaluated for the final formulation. However, the monomer 2-hydroxyoctanoic acid has long been used in topical applications [11] and was positively reviewed by the FDA [12]. Until now, hexPLA was mainly synthesized by ring-opening polymerization (ROP); the method that is actually used to produce biomedical grade PLA because it yields polymers with controlled molecular weights and narrow polydispersities [13]. Unfortunately, for ROP, dilactides as monomers must first be synthesized and purified before the final PLA polymerization. Furthermore, the residual dilactides remaining in the polymer even after extensive purification might influence the degradation characteristics [14], release profile [15], or even decrease the stability of the incorporated drug during formulation or storage [16]. For ROP of pharmaceutical PLA excipients, tin(II) 2-ethylhexanoate is generally used as catalyst of which 20–50 ppm remain in the final product [17]. Since tin catalysts were reported to show toxicological problems [18], a reduction or entire avoidance of this compound would be favorable. The melt polycondensation of 2-hydroxyoctanoic acid would be a more direct and economical way to produce hexPLA, avoiding the synthesis of the intermediate dilactide, the use of solvents, and allowing the use of pharmaceutical acceptable catalysts, if needed at all. In general, an often mentioned disadvantage of the polycondensation method is the limitation to lower molecular weight products with higher polydispersities in comparison with ROP [1], even if these characteristics are not of disadvantage for the intended injectables. Nevertheless, Hiltunen et al. successfully synthesized PLA in a one-step polycondensation with molecular weights up to 33,000 g/mol [19]. Recently, the melt polycondensation of 2-hydroxyacids with various side chains was reported, but only polymers with low molecular weights up to 2000 g/mol were obtained [20]. Here, we address the challenge to synthesize significantly higher molecular weight polymers of 2-hydroxyoctanoic acid by an efficient melt polycondensation and purification method. Furthermore, we investigated possibilities to improve the economical and ecological aspects of the synthesis method to produce polymers of high quality for pharmaceutical applications.

An additional aspect of this work deals with the use of the synthesized hexPLA as a potential excipient for parenteral sustained-release applications. Important characteristics for the usage as an injectable carrier were investigated such as the possibility to sterilize the product, its rheological properties, and injectability. Because of its liquid aggregate state and high lipophilicity, hexPLA can dissolve lipophilic substances, and the resulting formulations are clear solutions as previously shown by the authors [21]. In the present publication, the incorporation capacity and compatibility of different drugs were screened toward best formulation candidates for further investigations. Loratadine, an antihistaminic drug, was selected for further release experiments because of the clinical need for a sustained-release formulation. The release from a solution formulation with high drug loading was determined under *in vitro* conditions.

2. Materials and methods

2.1. Materials

Heptaldehyde and tin(II) 2-ethylhexanoate were purchased from Sigma Aldrich (St. Louis, USA) and sulfuric acid 96% from Acros Organics (New Jersey, USA). Cetirizine dihydrochloride, Loratadine, and Risperidone came from Molekula Deutschland (Taufkirchen, Germany) and Diclofenac sodium, Haloperidol, Ibuprofen sodium, Lidocaine hydrochloride, Metoprolol tartrate, Prednisolone 21-acetate, and N-methyl-2-pyrrolidone (NMP) from Sigma Aldrich (St. Louis, USA). Paracetamol was purchased from Hänseler (Herisau, Switzerland). All starting materials and solvents were used as received.

2.2. Methods

2.2.1. Polymerization and purification

The monomer 2-hydroxyoctanoic acid was synthesized from heptaldehyde, as published previously [8]. The melt polycondensations were performed in batch sizes between 2.5 g and 25.0 g. The monomer and, if used, a catalyst, tin(II) 2-ethylhexanoate or sulfuric acid, were added to a round bottom flask. The reactions were run for preset times and temperatures ranging from 120 °C to 180 °C under permanent stirring and vacuum, which was increased from normal pressure to the final 0.001 bar during the first 30 min of the synthesis. After cooling, the reaction mixture was dissolved in small amounts of acetone and precipitated into ethanol for the synthesis with tin(II) 2-ethylhexanoate or into a 0.1 M $NaHCO_3$ aqueous solution for the reactions with sulfuric acid. The precipitate was dissolved in acetone and filtered over silica gel before distilling off the solvent. The products of the synthesis without catalyst were not further purified after the melt polycondensation reaction.

2.2.2. Molecular weight and polydispersity determination

The molecular weights were determined by gel permeation chromatography (GPC) using a Waters 515 HPLC pump connected to a Waters 410 injector, Styragel HR 1-4 columns (Waters Corporation, Milford, USA), and Waters 717 GPC-detector (Waters Corporation, Milford, USA). THF was the continuous phase, and polystyrene standards (PSS, Mainz, Germany) were used for calibration. Product purity was controlled by ^{1}H NMR (300 MHz, Bruker).

2.2.3. Sterilization

Polymers synthesized with sulfuric acid catalysis were sterilized for 2 h at 160 °C according to the standard dry heat method recommended by the European Pharmacopoeia. The molecular weight was measured before and after sterilization to investigate the effect of dry heat sterilization on the polymer properties.

2.2.4. Formulation preparation

The formulations were simply prepared by mixing the hexPLA together with the intended amount of drug or NMP at room temperature in small plastic bags (Minigrip, Kennesaw, USA) until homogenous formulations were obtained. In the case of the incorporation capacity test, the formulation step was performed at 37 °C and the drugs were consecutively added until the maximal solubility was exceeded. The non-dissolved part of the drug was separated from the solution formulation by precipitating it under centrifugation at 12,300 g for 20 min.

2.2.5. Rheology

Rheological tests were carried out on a Bohlin Instruments CVO 120 stress rheometer with a parallel plate, type 20 mm (Bohlin Instruments, Cranbury, USA). For the investigation of the relation between shear rate and viscosity, the temperature was kept constant at either 25 °C or 37 °C. Shear rates from 0.1–1000 s^{-1}, delay times of 3 s, and integration times of 5 s were used. The relation between temperature and viscosity was assessed at a constant shear of 5 s^{-1} and temperatures from 10 °C to 37 °C.

2.2.6. Injectability

For the injection tests, the formulations were filled into 2-mL Luer-Lock-syringes, having a plunger diameter of 10.2 mm, and equipped with needles of 18 G width and 50 mm length. The syringes were fixed in a press type RM 50 (Schenck AG, Nänikon,

Switzerland) and the formulation ejected at a plunger speed of 5 mm/min, referring to an ejection volume of 0.4 mL/min. During the ejection process, the temperature was maintained at 18 °C and the force needed to push the formulation out of the syringe was recorded using an HBM Load Type 23H2 (Hottinger Baldwin Messtechnik, Volketswil, Switzerland).

2.2.7. Incorporation capacity determination

The incorporation capacity was determined by UV spectroscopy using a Cintra 404 UV/Vis-spectrophotometer (GBC, Braeside, Australia). HexPLA of 1800 g/mol, 2500 g/mol, and 5000 g/mol in isopropanol was used to determine the baseline absorption of the carrier in the range between 205 and 400 nm. For all drugs, the absorption maximum was measured and five point calibration curves were performed with correlation coefficients higher than 0.998. The actual drug incorporation was determined by dissolving the solution formulation in isopropanol and measuring the UV-absorption at the previously fixed wavelength. For each drug and polymer molecular weight, four samples of the clear drug-polymer solution were investigated.

2.2.8. Differential scanning calorimetry (DSC)

A DSC/2200C (Seiko Instruments, Tokyo, Japan) was used to obtain differential scanning curves of pure Loratadine, hexPLA polymers and of suspensions and solutions, respectively of Loratadine in hexPLA. The temperature ranged from −80 °C to 150 °C, and a heating rate of 5 °C was applied.

2.2.9. Sustained drug release investigation

The drug release was performed in phosphate buffered saline pH 7.4, containing additionally 0.02 M of sodium dodecyl sulfate (SDS) to increase the solubility of Loratadine at pH 7.4, which would otherwise be too low to perform a release experiment [22]. The maximal solubility of Loratadine in this buffer tempered at 37 °C was measured to be 0.68 mg/mL. Thus, the release could be performed under sink conditions up to a concentration of 0.2 mg/mL. The experiment was initiated by placing 50 mg of the Loratadine–hexPLA formulations into 100 mL of PBS buffer. At each sampling point, 1 mL of the release medium was taken from the samples and the volume replaced with fresh PBS buffer. The concentration of Loratadine was determined by UV/Vis-spectroscopy at 246 nm after previous calibration. For comparison, the dissolution of the pure drug in PBS buffer was investigated as well.

3. Results and discussion

3.1. Synthesis of HexPLA

Three different catalysts were investigated in this study, starting with today's standard catalyst for the production of pharmaceutical quality PLA and PLGA: tin(II) 2-ethylhexanoate. Despite its common use, tin(II) 2-ethylhexanoate, like many metal catalysts, causes toxicological problems [18] shifting interest toward other catalysts. Proton acids, like sulfuric acid, or even catalyst-free systems are interesting alternatives because they are pharmaceutically acceptable and were therefore also investigated in this study.

3.1.1. Tin(II) 2-ethylhexanoate catalyzed melt polycondensation

Since tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) is currently used in the production of poly(lactic acid) for numerous pharmaceutical products and medical devices, which are approved by the FDA [13], it is a first choice catalyst if the prepared polymers are to be used in biomedical applications. During the first 16 h of a 12 g scale polycondensation using tin(II) 2-ethylhexanoate (0.5 mol%) as the catalyst at 180 °C, the molecular weight of hexPLA increases linearly

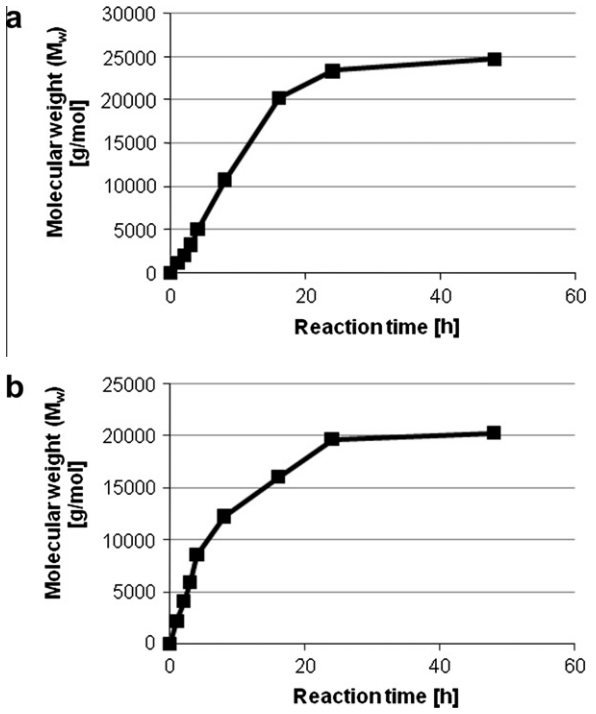

Fig. 1. Increase in molecular weight during melt polycondensation of hexPLA with (a) 0.5 mol% tin(II) 2-ethylhexanoate as catalyst; (b) 0.5 mol% sulfuric acid as catalyst.

(Fig. 1a). The weight-average molecular weight (M_w) was 1120 g/mol after 1 h, 5070 g/mol after 4 h, and 20,220 g/mol after 16 h, and it did not exceed 25,000 g/mol for longer reaction times. We assume this limitation is due to the insufficient condensation water removal from the viscous melt, which is diminished by the stirring capability of the magnetic stir bar in the melt. The M_w for the smaller 2.5 g scale reaction under the same reaction conditions led to 53,190 g/mol after 24 h (Table 1). Catalyst concentrations higher than 0.5 mol% did not result in higher molecular weights; in contrast, the M_w was reduced to 38,260 g/mol for a reaction with 2.0 mol% under the same conditions (Table 1). Catalyst concentrations that are too high can possibly lead to more side reactions, like chain scission and degradation reactions. The catalyst concentration had no effect on the polydispersities (PD), which were around 1.5 for all reactions, presumably controlled by the precipitation conditions. For comparison, the highest obtained M_w of 2-hydroxyoctanoic acid $Sn(Oct)_2$-catalyzed melt polycondensation is higher than that for the lactic acid polycondensation (33,000 g/mol) reported by Hiltunen et al. [19]. It has to be pointed out that a time dependent molecular weight control for hexPLAs up to 20,000 g/mol was possible. A general remaining drawback of a $Sn(Oct)_2$-catalyzed polycondensation is the necessity of organic solvents, methanol or ethanol, for the removal of the catalyst. Furthermore, although accepted by the health authorities, the small amounts of metal catalyst remaining in the product display toxicological problems for pharmaceutical applications. All melt polycon-

Table 1
HexPLA melt polycondensation with different amounts of tin(II) 2-ethylhexanoate as catalyst (24 h reaction time, 180 °C, 2.5 g batch size).

Catalyst concentration (mol%)	M_n (g/mol)	M_w (g/mol)	M_w/M_n
0.50	35,060	53,190	1.52
0.75	31,170	47,510	1.52
1.00	29,320	42,410	1.45
2.00	25,160	38,260	1.52

densations yielded viscous and clear but yellow-colored polymers, appearing more pronounced with harsher reaction conditions. Different purification methods were tested, but no quantitative discoloration could be achieved.

3.1.2. Sulfuric acid catalyzed melt polycondensation

Sulfuric acid was investigated as an alternative catalyst to allow an entirely "green chemistry." Its superior water solubility was expected to facilitate polymer purification by precipitation into water, the most favorable solvent, because of its non-toxicity as well as environmental and economical advantages. Under slightly basic conditions (with the addition of 0.1 M $NaHCO_3$), non-reacted monomers become water soluble and can be fully removed. Indeed, all melt polycondensations catalyzed with sulfuric acid and "aqueous-purification" led to pure, clear, and colorless polymers.

To optimize the sulfuric acid catalyzed melt polycondensations of 2-hydroxyoctanoic acid, different initial reaction temperatures were tested with regard to polymer molecular weights. For a reaction time of 6 h, the time at which $Sn(Oct)_2$-catalyzed reactions lead to controlled M_w, and a mean batch size of 7.0 g and a reaction temperature of 150 °C led to the highest M_w of 11,820 g/mol (Table 2). Higher reaction temperatures of 180 °C led to a similar M_w, but proved unfavorable because of the yield of crude products with higher impurities. A lower reaction temperature of 120 °C led to a significant decrease in M_w (7000 g/mol). As observed for $Sn(Oct)_2$, the catalyst concentration of sulfuric acid also influences the M_w. Concentrations of sulfuric acid lower and higher than 0.5 mol% led to notably decreased M_w. Larger batches (21.0 g in comparison with 7.0 g) gave lower M_w, a similar result as found for $Sn(Oct)_2$ and caused possibly by the same reasons of constricted polycondensation water removal from the melt. It must be pointed out that sulfuric acid-catalyzed melt polycondensations also facilitate the synthesis of defined molecular weights by controlling the reaction time (Fig. 1b). A linear increase in M_w was observed during the first 6 h, followed by a reduced M_w-increase and leading to a M_w maximum of 20,000 g/mol for longer reaction times. For all sulfuric acid-catalyzed melt polycondensations, high yields of 90% of pure hexPLAs were obtained after the aqueous precipitation and purification procedure.

3.1.3. Melt polycondensation without any catalyst

The most favorable synthesis method would be an entirely catalyst-free system. Therefore, a reaction with a 15 g batch of 2-hydroxyoctanoic acid was performed without the use of any additional catalyst. At 150 °C, the reaction resulted in a clear, pure, and colorless polymer after a reaction time of 8 h. Shorter reaction times of 1 h, 2 h, and 4 h did not yet lead to a total conversion of the monomer. The final M_w after 8 h was 1800 g/mol and the PDI 1.5. Thus, longer reaction times are needed and lower molecular weights are obtained for the auto-catalyzed polymerization of 2-hydroxyoctanoic acid in comparison with the catalysis with sulfuric acid or tin(II) 2-ethylhexanoate. However, this synthesis method is interesting for the preparation of low molecular weight polymers for biomedical use as for example direct injectables since no further purification step is necessary due to the absence of any additional material than the monomer.

Table 2
HexPLA melt polycondensation with sulfuric acid as catalyst (6 h reaction time, 7.0 g batch size).

Temperature (°C)	Catalyst (mol%)	M_n (g/mol)	M_w (g/mol)	M_w/M_n
120	0.50	4430	7000	1.58
150	0.50	8140	11,820	1.45
180	0.50	7480	10,670	1.43
150	0.16	2240	3600	1.61
150	0.80	3620	7100	1.96

3.2. Characterization of hexPLA as an excipient for parenterals

3.2.1. Sterilizability

A key factor for the use of novel polymers for parenteral sustained-release formulations is the possibility to sterilize them, preferably with standard sterilization techniques already accepted by the health authorities. It is obviously not possible to autoclave hexPLA because of the cleavage of the ester bonds in the presence of water, and gas sterilization could result in a reaction of the polymer with the agent. Thus, gamma-, electron beam-, and X-ray radiation, as well as dry heat sterilization are feasible methods. In this context, dry heat is the technique of choice because of its simplicity and the possibility to generally perform the sterilization step in house instead of at a contractor site. HexPLA polymers of different molecular weights were dry-heat sterilized by a standard dry-heat method recommended by the Ph. Eur. for 2 h at 160 °C. To investigate whether the sterilization step influences the properties of the hexPLA polymer, for example by degradation of the polymer chain as observed for poly (L-lactide) [23], the molecular weight was determined before and after the sterilization. Fig. 2 displays the values of the molecular weight after sterilization over the values before sterilization. The correlation coefficient for the linear regression line is 0.97, and its good compliance with the theoretical line of stability illustrates that the sterilization process did not affect the stability of the polymer. All polymers in the range between 1500 g/mol and 25,000 g/mol were stable toward degradation or chain growth. The good stability of hexPLA synthesized with sulfuric acid as catalyst regarding heat in comparison with classical PLA is due to the absence of metal catalysts, which can promote chain scissoring reactions.

3.2.2. Polymer rheology characterization

Although the maximum molecular weights are lower for the sulfuric acid and catalyst-free polymerizations compared to those of $Sn(Oct)_2$, the hexPLA polymers show interesting characteristics for use as pharmaceutical carrier materials regarding their rheological properties. The polymers have an ideal viscous behavior in the range between 0.1 s^{-1} and 150 s^{-1} for all molecular weights as is shown in Fig. 3. At shear rates exceeding 150 s^{-1}, hexPLA shows shear thinning and thixotropic characteristics with fast return to initial values. This behavior is more pronounced for polymers with high molecular weight because the alignment of the longer linear polymer chains along the direction of shear more significantly reduces interaction. The viscosity values of all hexPLAs are furthermore highly temperature dependent as illustrated in Fig. 4. Increasing the polymer temperatures from 10 °C to 37 °C reduces

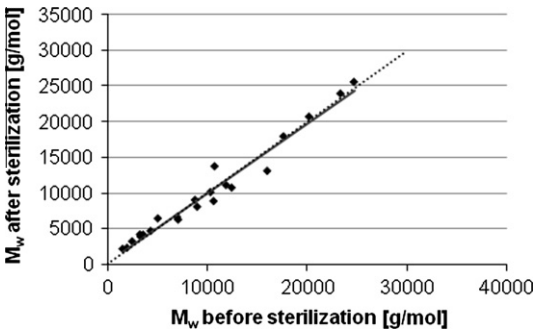

Fig. 2. Comparison of the molecular weight of hexPLA before and after dry heat sterilization (continuous line = regression line; dashed line = theoretical line of stability).

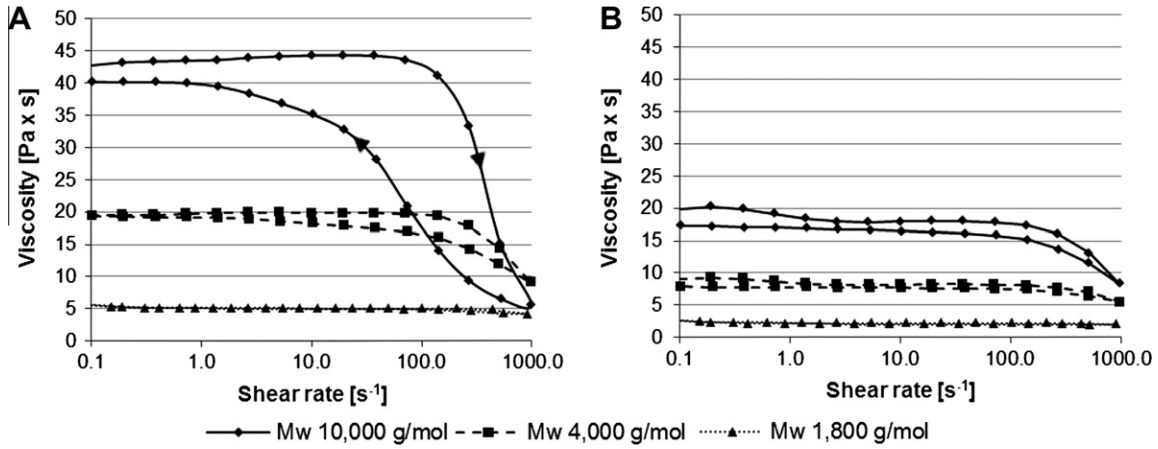

Fig. 3. Rheological behavior of hexPLA polymers in the range between 0.1 and 1000 s^{-1} at 25 °C (A) and 37 °C (B).

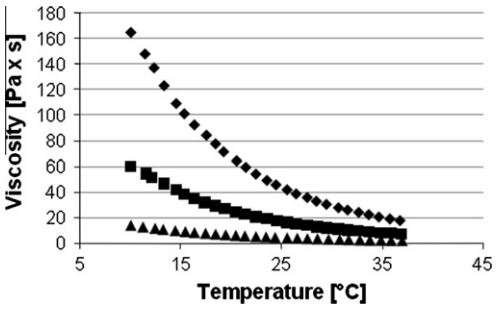

Fig. 4. Viscosity of different hexPLA polymers in the ideal viscous range (0.1–100 s^{-1}) in dependence of the temperature (♦ = M_w 10,000 g/mol; ■ = M_w 4500 g/mol; ▲ = M_w 1800 g/mol).

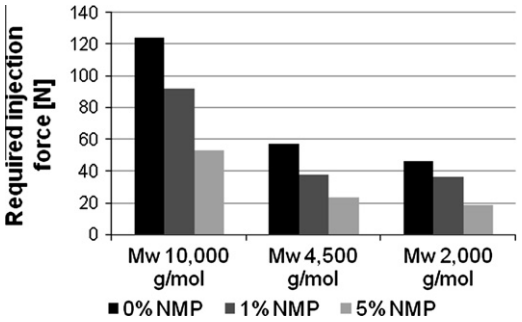

Fig. 5. Force needed for injection of different hexPLA molecular weight polymers with 0%, 1%, and 5% (w/w) NMP, respectively incorporated (18 G-, 50 mm-needle, 2-mL syringe).

the viscosity to around 10% of the initial value. Practically, the injectability of a pharmaceutical formulation using hexPLA could be increased by slightly warming up the product before application. Another advantage especially for suspension formulations is that storage at reduced temperatures can inhibit precipitation of the incorporated drug during the storage period.

Differential scanning calorimetry curves were taken of the pure polymers to investigate the glass transition temperature. A comparison of hexPLA polymers with ascending M_w shows an increase in the glass transition temperature from −45.6 °C for a polymer of 1800 g/mol, to −40.7 °C for 2500 g/mol, up to −39.6 °C for 5000 g/mol. This increase is due to the stronger interaction between the polymer molecules with longer chain length, and it is in accordance with the higher viscosity for longer chains.

While the low viscosity of the polymers with low molecular weight allows easy application, higher molecular weight polymers may pose problems during injection. Thus, the injectability of these polymers was studied in detail.

3.2.3. Injectability

According to the law of Hagen–Poiseuille, the force needed for injection depends not only on the viscosity of the formulations but also on the syringe diameter, injection speed, length of the needle, and especially the inner needle diameter. The lack of common standards and limits for these parameters hampers the grading of injection ease. We applied standard 2-mL syringes and 18 G needles, which are actually thinner than needles used for implant application. The injection speed was fixed at 0.4 mL/min to allow the application of a reasonable 100 mg of formulation in 15 s. Injection forces as high as 300 N were reported as the upper limit and 90–120 N rated as adequate for injection [24]. However, the lower limits given by Rungseevijitprapa and Bodmeier are more reasonable and were applied for the evaluation of hexPLA. They define injection forces of less than 50 N to be injectable without difficulties [25]. The rheological data suggest easy injectability of low molecular weight hexPLA polymers but more difficult injection for higher molecular weights due to increasing viscosity. This presumption was underlined by the injection tests as shown in Fig. 5. The pure polymer having a molecular weight of 2000 g/mol was easily injectable by hand; however, the possibilities had to be studied to make high molecular weight hexPLA injectable in case simple warming to reduce the viscosity is not feasible. The use of high molecular weight hexPLA may be interesting if long release periods are intended, since the degradation period is directly linked to the initial molecular weight of a polyester. An approach to improve the injectability is the addition of plasticizers. A number of plasticizers have been proposed for PLA including poly(ethylene glycol), glycerol, citrate ester [26], triacetine [27], or even drugs themselves [28]. HexPLA itself showed to be mixable with biocompatible liquids acting as plasticizers like ethanol, dimethylsulfoxide (DMSO), and poly (ethylene glycol) 550 monomethyl ether (MPEG 550). Among the plasticizers, N-methyl-2-pyrrolidone (NMP) was especially interesting because it is used in the marketed Atrigel® technology to dissolve PLA for injectable *in vivo* precipitating implants [29]. A product based on this technology is Eligard®, an injectable sustained-release formulation of Leuprolide, in which up to 66% of NMP is needed to make the formulation injectable. For higher M_w hexPLAs in contrast, only 1–5% of NMP was sufficient to significantly reduce the injection force to acceptable levels below 40 N. The amount of plasticizer needed to obtain easily injectable

formulations depends on the initial viscosity and thus, on the molecular weight of the polymer.

3.3. Drug dissolution and incorporation capacity

Due to its liquid aggregate state and high lipophilicity, hexPLA is able to dissolve lipophilic substances [21]. The resulting solutions are interesting for pharmaceutical applications because many problems related to suspensions can be avoided with solutions, like precipitation of the drug during storage and caking in the needle. Also, the formulation process is simpler because parameters like particle size distribution can be omitted. For parenteral sustained-release formulations, a high incorporation capacity of the drug in the formulation is important since the maximal applicable volume is limited, depending on the site of application. To identify possible candidates, the incorporation capacity of several drugs was assessed in directly injectable polymers of molecular weights between 1800 g/mol and 5000 g/mol. Since initial experiments had shown a dependency between temperature and incorporation capacity, the temperature was fixed at 37 °C. The solubilities ranged from very slightly soluble as for Paracetamol to freely soluble as for Haloperidol, Ibuprofen, Lidocaine, and Loratadine. For a large number of lipophilic drugs, the solubility in hexPLA increased with decreasing molecular weight of the hexPLA polymer as displayed in Fig. 6. Accordingly, hexPLA becomes more "solvent like" at low molecular weights because it is less viscous and can incorporate more of the lipophilic drugs. Since Loratadine had a high incorporation capacity among the investigated drugs together with a strong efficacy *in vivo* [30], it was selected for further solubility and release experiments.

The complete dissolution of an active substance in hexPLA was verified by differential scanning calorimetry on the example of a suspension of Loratadine in hexPLA of 1800 g/mol. Fig. 7 shows the pure drug (D), having a melting point at 133 °C and the pure hexPLA polymer (A) with a glass transition temperature at −46 °C. A freshly prepared suspension containing 50% (w/w) Loratadine in hexPLA shown in curve C, leads to an increased glass transition temperature in comparison with the pure polymer. The melting point of the active substance is less pronounced than for the pure substance, and it is shifted toward lower temperatures. A second heating cycle of this mixture is displayed in curve B, showing a further increase in the glass transition temperature of the hexPLA–Loratadine mix. The absence of any melting point for the drug proves the entire dissolution of the lipophilic compound in the matrix. Accordingly, a super-saturated solution containing 50% Loratadine in hexPLA 1800 g/mol was prepared. Super-saturated drug–hexPLA solutions showed to be stable for several days depending on the excess amount of incorporated substance and polymer molecular weight before recrystallization of the active compound. The increase in the glass transition temperature with cumulative Loratadine concentration is due to a solidifying effect

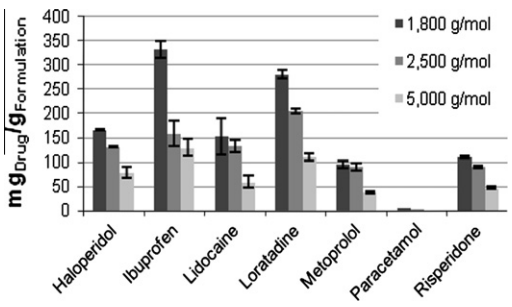

Fig. 6. Maximum solubility of different drugs in hexPLA of molecular weights between 1800 g/mol and 5000 g/mol determined by UV/Vis-spectroscopy, $n = 4$.

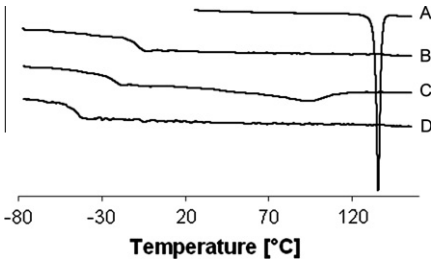

Fig. 7. DSC curves of: (A) pure crystalline Loratadine; (B) Loratadine dissolved in hexPLA; (C) Loratadine suspension in hexPLA; (D) pure hexPLA of 1800 g/mol.

of the active substance. This effect also causes an increase in viscosity from 5 Pa s at 25 °C for the neat polymer of 1800 g/mol to 155 Pa s for a formulation containing the maximum drug loading of 28% Loratadine, which might provoke problems regarding injectability. If a drug loading to such an extend is necessary, the formulation could either be warmed to 37 °C and thereby the viscosity reduced to 40 Pa s or small amounts of plasticizers could be added as demonstrated above. In addition, the high drug loading and drug efficacy result in a low amount of formulation needed to be administered. It has to be pointed out that such high drug loadings of more than 20% are usually not possible using classical solid implants because the drug is rapidly being washed out without additional coatings [31].

3.4. In vitro Loratadine release from hexPLA formulations

Loratadine was selected as a model drug not only because of its good solubility in hexPLA but also because of its high efficacy and good tolerability [30]. Both factors are important for sustained-release formulations because it is sufficient to apply small amounts and slight unsteadiness in release can be tolerated. To our knowledge, despite these beneficial characteristics, no parenteral sustained-release formulation of Loratadine or of any other H_1 -antihistaminic is marketed. In contrast, there is a high prevalence of allergic diseases in developed countries, with 10% of the adult population and more than 25% of children being affected [32]. Together with the low compliance and the so-called allergic march, the worsening of allergies due to insufficient treatment, these facts demonstrate the clinical need for a long term sustained-release formulation of Loratadine.

Loratadine was completely and immediately soluble in the PBS buffer with 0.02 M SDS at 37 °C. In contrast, a formulation of 28% Loratadine in hexPLA of 1800 g/mol slowly released the active substance during a period of 14 days, as shown in Fig. 8. The release is showing a zero order kinetic with a high correlation coefficient for

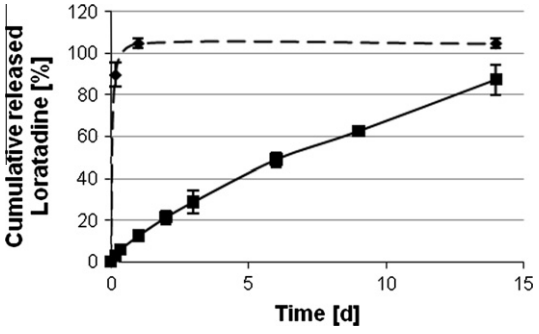

Fig. 8. Dissolution of Loratadine in PBS buffer (dashed line) and release of Loratadine from a 50 mg solution formulation with 28% Loratadine in hexPLA of 1800 g/mol (solid line), $n = 3$.

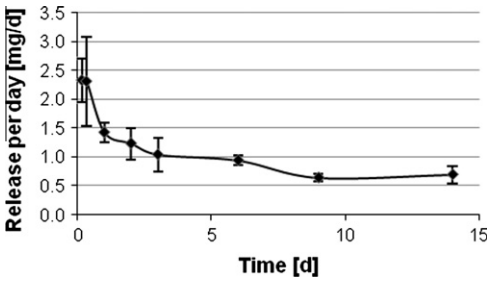

Fig. 9. Release per day of Loratadine from a Loratadine–hexPLA formulation (50 mg formulation containing 28% Loratadine in hexPLA of 1800 g/mol, $n = 3$).

a linear regression of 0.98. Accordingly, the drug release per day is varying over time only in a small range as displayed in Fig. 9. It has to be pointed out that despite of its high drug loading of 28%, the formulation showed neither a pronounced burst release nor a lag phase. The deviation in the total release was low with values smaller than 7.5% for all sampling points, proving that hexPLA formulations release with good reproducibility. After 21 days, the drug was entirely released from the formulation and the formulation droplet was totally degraded. The SDS added to the PBS buffer to obtain sink conditions of the Loratadine may increase the dissolution rate of the drug and the hexPLA degradation products like 2-hydroxyoctanoic acid monomers and small hexPLA oligomers. Thus, the release rate compared to a pure aqueous buffer might be slightly higher and the *in vitro* release experiment could underestimate the period of release compared to *in vivo* behavior. However, the liquid aggregate state of the formulation, together with the zero order release and degradation, suggests a release mechanism, which is mainly driven by surface erosion.

In the context of Loratadine treatment for allergic rhinitis, 10 mg has to be administered per day when using immediate release formulations due to its short half life time of around 4 h [33]. For sustained-release formulations, lower drug amounts are needed because of the more constant release. Thus, the 50 mg of hexPLA solution formulation, releasing 14 mg of Loratadine over 2 weeks, may already be a considerably applicable formulation, especially because of the low amount of formulation and favorable drug to carrier ratio. Certainly, the encouraging findings from our *in vitro* studies have to be verified in *in vivo* experiments.

4. Conclusion

The melt polycondensation of 2-hydroxyoctanoic acid is a suitable method to synthesize viscous hydrophobic hexPLA excipients. Using tin(II) 2-ethylhexanoate as catalyst yielded the highest molecular weights, but high molecular weight polymers are less favorable regarding injectability and drug incorporation than polymers with shorter chain lengths. These lower molecular weight hexPLAs can easily be prepared by a sulfuric acid catalyzed or an entirely catalyst free "green chemistry" synthesis. All polymers prepared by these methods are stable during dry-heat sterilization. Lipophilic drugs can easily be incorporated by mixing and dissolution, resulting in viscous formulations, which represent a new concept for parenteral sustained-release formulations. In certain cases, the drug acts as solidifier, increasing the viscosity of the solutions, but the injectability of the formulations can be improved by slightly warming or adding small amounts of plasticizers like NMP. Stable solution formulations with drug loadings of up to 33% can be prepared, depending on the solubility of the compound. Despite the high drug loading of the formulation, a zero order release can be achieved, presumably generated by surface erosion. Due to high drug loading in hexPLA and the potency of the active compound, small amounts of formulation are sufficient to achieve long release periods, as was demonstrated with Loratadine –hexPLA solution formulations. HexPLA polymers are interesting for parenteral sustained-release formulations of lipophilic drugs, which are soluble in the matrix and for which a constant release period of several days to weeks is intended.

References

[1] T. Maharana, B. Mohanty, Y.S. Negi, Melt-solid polycondensation of lactic acid and its biodegradability, Prog. Polym. Sci. 34 (2009) 99–124.
[2] A. Sodergard, M. Stolt, Properties of lactic acid based polymers and their correlation with composition, Prog. Polym. Sci. 27 (2002) 1123–1163.
[3] R.E. Drumright, P.R. Gruber, D.E. Henton, Polylactic acid technology, Adv. Mater. 12 (2000) 1841–1846.
[4] B. Gupta, N. Revagade, J. Hilborn, Poly(lactic acid) fiber: an overview, Prog. Polym. Sci. 32 (2007) 455–482.
[5] S.G. Wang, W.J. Cui, J.Z. Bei, Bulk and surface modifications of polylactide, Anal. Bioanal. Chem. 381 (2005) 547–556.
[6] J.C. Middleton, A.J. Tipton, Synthetic biodegradable polymers as orthopedic devices, Biomaterials 21 (2000) 2335–2346.
[7] Y. Ikada, H. Tsuji, Biodegradable polyesters for medical and ecological applications, Macromol. Rapid Commun. 21 (2000) 117–132.
[8] T. Trimaille, R. Gurny, M. Moller, Synthesis and properties of novel poly(hexyl-substituted lactides) for pharmaceutical applications, Chimia 59 (2005) 348–352.
[9] W.P. Cheng and A.J. Tipton, Composition, US Patent 0029,544, 2010.
[10] T. Trimaille, R. Gurny, M. Moller, Poly(hexyl-substituted lactides): novel injectable hydrophobic drug delivery systems, J. Biomed. Mater. Res. A 80A (2007) 55–65.
[11] M.E. Kraeling, R.L. Bronaugh, *In vitro* percutaneous absorption of alpha hydroxy acids in human skin, J. Soc. Cosmet. Chem. 48 (1997) 187–197.
[12] US Food and Drug Administration, Alpha Hydroxy Acids in Cosmetics. http://www.fda.gov/Cosmetics/ProductandIngredientSafety/SelectedCosmeticIngredients/ucm107940.htm (page last updated 07/06/2009, page accessed 06/27/2011).
[13] T. Trimaille, M. Moller, R. Gurny, Synthesis and ring-opening polymerization of new monoalkyl-substituted lactides, J. Polym. Sci. Polym. Chem. 42 (2004) 4379–4391.
[14] S.H. Hyon, K. Jamshidi, Y. Ikada, Effects of residual monomer on the degradation of DL-lactide polymer, Polym. Int. 46 (1998) 196–202.
[15] B. Bittner, M. Morlock, H. Koll, G. Winter, T. Kissel, Recombinant human erythropoietin (rhEPO) loaded poly(lactide-co-glycolide) microspheres: influence of the encapsulation technique and polymer purity on microsphere characteristics, Eur. J. Pharm. Biopharm. 45 (1998) 295–305.
[16] A. Rothen-Weinhold, N. Oudry, K. Schwach-Abdellaoui, S. Frutiger-Hughes, G.J. Hughes, D. Jeannerat, U. Burger, K. Besseghir, R. Gurny, Formation of peptide impurities in polyester matrices during implant manufacturing, Eur. J. Pharm. Biopharm. 49 (2000) 253–257.
[17] A. Stjerndahl, A. Finne-Wistrand, A.C. Albertsson, C.M. Backesjo, U. Lindgren, Minimization of residual tin in the controlled Sn(II)octoate-catalyzed polymerization of epsilon-caprolactone, J. Biomed. Mater. Res. A 87 (2008) 1086–1091.
[18] H.R. Kricheldorf, H. Hachmann-Thiessen, Copolymerization of epsilon-caprolactone and glycolide – a comparison of bismuth(III) hexanoate and tin(II) octanoate as initiators, J. Polym. Sci. Polym. Chem. 43 (2005) 3268–3277.
[19] K. Hiltunen, J.V. Seppala, M. Harkonen, Effect of catalyst and polymerization conditions on the preparation of low molecular weight lactic acid polymers, Macromolecules 30 (1997) 373–379.
[20] N. Cohen-Arazi, J. Katzhendler, M. Kolitz, A.I. Domb, Preparation of new alpha-hydroxy acids derived from amino acids and their corresponding polyesters, Macromolecules 41 (2008) 7259–7263.
[21] L.R. Asmus, R. Gurny, M. Moller, Solutions for lipophilic drugs – a biodegradable polymer acting as solvent, matrix, and carrier to "solve" drug delivery issues, Int. J. Artif. Organs 34 (2011) 238–242.
[22] G. Popovic, M. Cakar, D. Agbaba, Acid–base equilibria and solubility of loratadine and desloratadine in water and micellar media, J. Pharmaceut. Biomed. 49 (2009) 42–47.
[23] O. Wachsen, K. Platkowski, K.H. Reichert, Thermal degradation of poly-L-lactide – studies on kinetics, modelling and melt stabilisation, Polym. Degrad. Stabil. 57 (1997) 87–94.
[24] U. Gbureck, J.E. Barralet, K. Spatz, L.M. Grover, R. Thull, Ionic modification of calcium phosphate cement viscosity. Part I: Hypodermic injection and strength improvement of apatite cement, Biomaterials 25 (2004) 2187–2195.
[25] W. Rungseevijitprapa, R. Bodmeier, Injectability of biodegradable in situ forming microparticle systems (ISM), Eur. J. Pharm. Sci. 36 (2009) 524–531.
[26] O. Martin, L. Averous, Poly(lactic acid): plasticization and properties of biodegradable multiphase systems, Polymer 42 (2001) 6209–6219.
[27] N. Ljungberg, B. Wesslen, The effects of plasticizers on the dynamic mechanical and thermal properties of poly(lactic acid), J. Appl. Polym. Sci. 86 (2002) 1227–1234.
[28] P. Blasi, A. Schoubben, S. Giovagnoli, L. Perioli, M. Ricci, C. Rossi, Ketoprofen poly(lactide-co-glycolide) physical interaction, AAPS PharmSciTech 8 (2007).

[29] R. Dunn, Application of the ATRIGEL® implant drug delivery technology for patient-friendly, cost-effective product development, Drug Deliv. Technol. 3 (2003).
[30] B.M. Prenner, D. Capano, A.G. Harris, Efficacy and tolerability of loratadine versus fexofenadine in the treatment of seasonal allergic rhinitis: a double-blind comparison with crossover treatment of nonresponders, Clin. Ther. 22 (2000) 760–769.
[31] G.J. Wang, I.G. Tucker, M.S. Roberts, L.W. Hirst, In vitro and in vivo evaluation in rabbits of a controlled release 5-fluorouracil subconjunctival implant based on poly(D,L-lactide-co-glycolide), Pharm. Res. 13 (1996) 1059–1064.
[32] H.W. Chu, C.M. Lloyd, W. Karmaus, P. Maestrelli, P. Mason, G. Salcedo, J. Thaikoottathil, A.J. Wardlaw, Developments in the field of allergy in 2009 through the eyes of clinical and experimental allergy, Clin. Exp. Allergy 40 (2010) 1611–1631.
[33] I.I. Salem, N.M. Najib, N.M. Idkaidek, A. Retrospective, Open-label analysis of the population pharmacokinetics of a single 10-mg dose of loratadine in healthy white Jordanian male volunteers, Clin. Ther. 32 (2010) 391–395.