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Research paper

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

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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

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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,