Polyketal Copolymers: A New Acid-Sensitive Delivery Vehicle for Treating Acute Inflammatory Diseases

Stephen C. Yang,‡ Mahesh Bhide,§ Ian N. Crispe,‡ Robert H. Pierce,‡,# and Niren Murthy*,†

Wallace H. Coulter Department of Biomedical Engineering and Parker H. Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, Georgia 30332, and David H. Smith Center for Vaccine Biology and Immunology and the Department of Pathology, University of Rochester, Rochester, New York 14627. Received November 30, 2007; Revised Manuscript Received April 8, 2008

Acute inflammatory diseases are a major cause of death in the world, and effective treatments are greatly needed. Macrophages play a central role in causing acute inflammatory diseases, and there is currently great interest in developing drug delivery vehicles that can target therapeutics to macrophages. Microparticles formulated from aliphatic polyketals have great potential to enhance the treatment of acute inflammatory diseases, due to their ability to passively target therapeutics to macrophages, their acid sensitivity, and their biocompatible degradation products. However, existing aliphatic polyketals are unsuitable for treating acute inflammatory diseases because they require weeks to hydrolyze, and strategies for accelerating their hydrolysis kinetics are greatly needed. In this report, we demonstrate that the hydrolysis kinetics of aliphatic polyketals can be accelerated by increasing their hydrophilic/hydrophobic balance. Aliphatic polyketals of varying hydrophobicity were synthesized, via the acetal exchange reaction, and their hydrolysis kinetics were investigated at the pH values of 4.5 and 7.4. A polyketal termed PK3 was developed, which had the hydrolysis kinetics suitable for treating acute inflammatory diseases. PK3 has a hydrolysis half-life of 2 days at pH 4.5, but requires several weeks to hydrolyze at pH 7.4. Microparticles were formulated with PK3, which encapsulated the anti-inflammatory drug, imatinib. In vivo experiments demonstrated that PK3 microparticles were able to significantly improve the efficacy of imatinib in treating acute liver failure. We anticipate that aliphatic polyketals will have numerous applications for the treatment of acute inflammatory diseases, given their pH sensitivity, tunable hydrolysis kinetics, and biocompatible degradation products.

INTRODUCTION

Acute inflammatory diseases such as acute lung injury and acute liver failure cause millions of deaths each year, and effective treatments are greatly needed (1, 2). Pro-inflammatory cytokines secreted by macrophages play a central role in mediating acute inflammatory diseases, and drug delivery vehicles that can target therapeutics to macrophages have great clinical potential (3). A key drug delivery requirement for the treatment of many acute inflammatory diseases is fast release of drugs to diseased organs, within several hours. This is because, at the time of patient diagnosis, significant tissue damage has already occurred, and organ function is rapidly deteriorating (4). It has been challenging to develop clinically acceptable drug delivery vehicles that can target therapeutics to macrophages and release them rapidly. Liposomes are a potential delivery vehicle for treating acute inflammatory diseases, due to their ability to target macrophages (5). However, their serum instability and poor storage properties have slowed their progress in clinical trials. Microparticles, based on biodegradable polymers, also have potential to enhance the treatment of acute inflammatory diseases. Microparticles can be freeze-dried, have an excellent shelf life, and can also passively target therapeutics to macrophages (6, 7). However, currently used biomaterials for drug delivery are predominantly based on polyesters, which are potentially problematic for treating acute inflammatory diseases because of their slow hydrolysis kinetics and acidic degradation products, which themselves frequently cause inflammation (8, 9).

Microparticles formulated from polyketals are a new drug delivery vehicle, which degrade into neutral compounds comprising acetone and diols, and should therefore avoid the inflammatory problems associated with polyester-based materials (9–13). At present, only two polyketals have been synthesized for drug delivery, poly(1,4-phenyleneacetone dimethylene ketal) (PPADK) and poly(cyclohexane-1,4-diyl acetone dimethylene ketal) (PCADK) (12, 13). PPADK has excellent hydrolysis kinetics for treating acute inflammatory diseases, having a half-life of 35 h at pH 5.0, but degrades into benzene dimethanol, a compound with potential toxicity, due to its aromatic ring. PCADK is an aliphatic polyketal, which degrades into acetone and 1,4-cyclohexanediol, both of which have excellent biocompatibility. However, PCADK has a hydrolysis half-life of 24 days at pH 4.5, which is too slow for applications involving the treatment of acute inflammatory diseases, and therefore strategies that can accelerate its hydrolysis kinetics are greatly needed.

In this report, we demonstrate that the hydrolysis kinetics of PCADK derived aliphatic polyketals can be accelerated by increasing their hydrophilic/hydrophobic balance. Using this principle, we were able to generate a polyketal copolymer, termed PK3, which had a hydrolysis half-life of 2 days at pH 4.5 but several weeks at pH 7.4. Microparticles formulated from PK3 should be suitable for treating acute inflammatory diseases because they should hydrolyze and release therapeutics rapidly in the phagolysosomes of macrophages, but remain stable at...
Numerous applications for the treatment of acute inflammatory diseases have been anticipated for aliphatic copolyketals. Based on the results of Lee et al. (13), imatinib-loaded PK3 microparticles significantly enhanced the delivery of imatinib in mice suffering from acute liver failure. PK3 microparticles were capable of enhancing the delivery of imatinib to liver macrophages and enhance the treatment of acute liver failure. PK3 is designed to deliver therapeutic payloads to liver macrophages and enhance the treatment of acute inflammatory diseases.

**EXPERIMENTAL SECTION**

**Materials.** All chemicals were purchased from Sigma-Aldrich (St. Louis, MO) and were used as received unless otherwise specified. Benzene and 2,2-dimethoxypropane were purified by distillation. Imatinib was a gift from Novartis.

**Animals.** Male C57BL/6 mice were purchased from Jackson Laboratory (Bar Harbor, ME). All animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Rochester Medical Center.

**Synthesis of Polyketal Copolymers.** Polyketal copolymers were synthesized in a 25 mL two-necked flask, connected to a short-path distilling head. The diols, 1,4-cyclohexanediol (1.04 g, 7.25 mmol) and 1,4-butandiol, 1,5-pentanediol, 1,6-hexanediol, or 1,8-octanediol, were dissolved in 20 mL of distilled benzene and kept at 100 °C. Recrystallized p-toluene-sulfonic acid (5.5 mg, 0.029 mmol) was dissolved in ethyl acetate (500 μL) and added to the benzene solution. The ethyl acetate was distilled off, and the polymerization reaction was initiated by the addition of 2,2-dimethoxypropane (equimolar to the two diols combined). Additional doses of 2,2-dimethoxypropane (500 μL) and benzene (2 mL) were subsequently added to the reaction, every hour for six hours, via a metering funnel, to compensate for 2,2-dimethoxypropane and benzene that had distilled off. After 24 h, the reaction was stopped with triethylamine (100 μL). The copolymers were isolated by precipitation into cold hexanes and analyzed by 1H NMR and GPC. In general, the resulting polymers had number average molecular weights between 2000 to 3000 Da. Table 1 lists the compositions and molecular weights of the polyketal copolymers synthesized. 1H NMR spectra were obtained from a Varian Mercury VX 400 MHz NMR spectrometer (Palo Alto, CA) using CDCl3 as the solvent. PK1 1H NMR (400 MHz, CDCl3, δ): 3.4–3.18 (m, 4H, CH2), 1.66 (s, 1.9H, CH), 1.85–0.93 (m, 8H, CH2), and 1.32 (s, 6H, CH3). PK2 1H NMR (400 MHz, CDCl3, δ): 3.4–3.18 (m, 4H, CH2), 1.66 (s, 1.8H, CH), 1.85–0.93 (m, 8H, CH2), and 1.32 (s, 6H, CH3). PK3 1H NMR (400 MHz, CDCl3, δ): 3.4–3.18 (m, 4H, CH2), 1.64 (s, 1.7H, CH), 1.85–0.93 (m, 8.2H, CH2), and 1.32 (s, 6H, CH3). PK4 1H NMR (400 MHz, CDCl3, δ): 3.4–3.18 (m, 4H, CH2), 1.68 (s, 2H, CH), 1.85–0.93 (m, 8H, CH2), and 1.32 (s, 6H, CH3). PK5 1H NMR (400 MHz, CDCl3, δ): 3.4–3.18 (m, 4H, CH2), 1.67 (s, 1.8H, CH), 1.85–0.93 (m, 8H, CH2), and 1.32 (s, 6H, CH3). PK6 1H NMR (400 MHz, CDCl3, δ): 3.4–3.18 (m, 4H, CH2), 1.68 (s, 1.8H, CH), 1.85–0.93 (m, 8H, CH2), and 1.32 (s, 6H, CH3).

**Gel Permeation Chromatography.** The molecular weights of the polyketal copolymers were determined by gel permeation chromatography (GPC) using a Shimadzu system (Kyoto, Japan) equipped with a UV detector. Tetrahydrofuran was used as the mobile phase at a flow rate of 1 mL/min. Polystyrene standards (peak Mw = 1060, 2970, and 10680) from Polymer Laboratories (Amherst, MA) were used to establish a molecular weight calibration curve.

**Hydrolysis of Polyketal Copolymers.** The hydrolysis of the polyketal copolymers was measured according to the procedures of Lee et al. (13). Briefly, polymer samples (20 mg) were placed in buffered water (1 mL) at the pH values of 4.5 (100 mM AcOH) and 7.4 (100 mM Na2HPO4) at 37 °C. The polymer samples were mixed by gentle shaking and, at specific time points, were extracted into CDCl3 (1 mL). The CDCl3 phase was isolated and analyzed by 1H NMR, to determine the percent hydrolysis.

**Release Kinetics of Rhodamine B from PK3 Microparticles.** Rhodamine B was encapsulated in PK3 microparticles using single emulsion procedures. Rhodamine B-loaded PK3 microparticles (10 mg) were suspended in pH 4.5 and pH 7.4 buffer solutions (10 mL). The suspensions were kept at 37 °C under gentle shaking. At specific time points, the suspensions (100 μL) were centrifuged at 10 000 rpm for 2 min to remove unhydrolyzed particles. The supernatant (3 μL) was then diluted in pH 7.4 buffer (3 mL), which was then analyzed by a Shimadzu spectrofluorophotometer (Kyoto, Japan) to quantify the relative concentration of rhodamine B released from the PK3 microparticles (excitation wavelength = 556 nm, emission wavelength = 573 nm).

**Formulation of Iminatinib-Loaded PK3 Microparticles.** Imatinib-loaded microparticles were formulated from PK3 using a modified water/oil/water emulsion method. Briefly, PK3 (100 mg) was dissolved in dichloromethane (1 mL), and in a separate vial imatinib (40 mg) was dissolved in deionized water (400 µL). The microparticles were prepared using single emulsion procedures. Rhodamine B was encapsulated in PK3 microparticles using single emulsion procedures. Rhodamine B-loaded PK3 microparticles (10 mg) were suspended in pH 4.5 and pH 7.4 buffer solutions (10 mL). The suspensions were kept at 37 °C under gentle shaking. At specific time points, the suspensions (100 μL) were centrifuged at 10 000 rpm for 2 min to remove unhydrolyzed particles. The supernatant (3 μL) was then diluted in pH 7.4 buffer (3 mL), which was then analyzed by a Shimadzu spectrofluorophotometer (Kyoto, Japan) to quantify the relative concentration of rhodamine B released from the PK3 microparticles (excitation wavelength = 556 nm, emission wavelength = 573 nm).
Table 1. Compositions and Molecular Weight of Polyketal Copolymers Synthesized

<table>
<thead>
<tr>
<th>polymer ID</th>
<th>monomer diol A (x)</th>
<th>monomer diol B (y)</th>
<th>Mw</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK1</td>
<td>1,4-cyclohexanediol (98.03%)</td>
<td>1,5-pentanediol (1.93%)</td>
<td>2149</td>
<td>1.742</td>
</tr>
<tr>
<td>PK2</td>
<td>1,4-cyclohexanediol (92.46%)</td>
<td>1,5-pentanediol (7.56%)</td>
<td>2530</td>
<td>1.629</td>
</tr>
<tr>
<td>PK3</td>
<td>1,4-cyclohexanediol (86.70%)</td>
<td>1,5-pentanediol (13.30%)</td>
<td>2596</td>
<td>1.432</td>
</tr>
<tr>
<td>PK4</td>
<td>1,4-cyclohexanediol (96.75%)</td>
<td>1,4-butanediol (3.25%)</td>
<td>2637</td>
<td>1.553</td>
</tr>
<tr>
<td>PK5</td>
<td>1,4-cyclohexanediol (85.32%)</td>
<td>1,6-hexanediol (14.68%)</td>
<td>2122</td>
<td>1.538</td>
</tr>
<tr>
<td>PK6</td>
<td>1,4-cyclohexanediol (87.31%)</td>
<td>1,8-octanediol (12.69%)</td>
<td>2181</td>
<td>1.786</td>
</tr>
</tbody>
</table>

* PDI: polydispersity index, calculated as the weight average molecular weight (Mw) divided by the number average molecular weight (Mn).

Table 2. Hydrolysis Half-Lives of Polyketal Copolymers at pH 4.5 and pH 7.4, at 37 °C

<table>
<thead>
<tr>
<th>polymer composition</th>
<th>diol A</th>
<th>percent diol A</th>
<th>diol B</th>
<th>percent diol B</th>
<th>half-life at pH 4.5</th>
<th>estimated half-life at pH 7.4</th>
<th>log P of diol B</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK4</td>
<td>1,4-cyclohexanediol</td>
<td>96.75%</td>
<td>1,4-butanediol</td>
<td>3.25%</td>
<td>1.0 day</td>
<td>54 days</td>
<td>-0.83</td>
</tr>
<tr>
<td>PK3</td>
<td>1,4-cyclohexanediol</td>
<td>86.70%</td>
<td>1,5-pentanediol</td>
<td>13.30%</td>
<td>1.8 days</td>
<td>53 days</td>
<td>0.27</td>
</tr>
<tr>
<td>PK5</td>
<td>1,4-cyclohexanediol</td>
<td>85.32%</td>
<td>1,6-hexanediol</td>
<td>14.68%</td>
<td>4.4 days</td>
<td>360 days</td>
<td>0.76</td>
</tr>
<tr>
<td>PK6</td>
<td>1,4-cyclohexanediol</td>
<td>87.31%</td>
<td>1,8-octanediol</td>
<td>12.69%</td>
<td>8.6 days</td>
<td>360 days</td>
<td>1.75</td>
</tr>
</tbody>
</table>

* log P is the logarithm of the water/octanol partition coefficient; the log P data were obtained from the Syracuse Research Corporation’s PhysProp Database.

Figure 1. Synthesis of polyketol copolymers from 1,4-cyclohexanediol, a second diol, and 2,2-dimethoxypropane. Hydrolysis kinetics of polyketols can be controlled by manipulating the hydrophilicity of the polykets through copolymerizing 1,4-cyclohexanediol with a more hydrophilic diol.

Determination of Imatinib Loading in PK3 Microparticles. The loading of imatinib in PK3 microparticles was determined by UV spectrometry. A UV calibration curve for imatinib was established at 268 nm, with a Shimadzu UV-1700 spectrometer (Kyoto, Japan) in pH 7.4 buffer. Imatinib-loaded PK3 particles were dissolved in a small amount of methylene chloride, and the imatinib was extracted into pH 7.4 buffer (100 mM Na2HPO4). The absorbance of both the aqueous and organic phases was measured to verify that all the imatinib was partitioned into the aqueous phase. The concentration of imatinib loaded into the PK3 microparticles was determined against the established calibration curve as mentioned above.

Treatment of Acute Liver Failure in Mice with Imatinib-Loaded PK3 Microparticles. Male C57/BL6 mice, 6–8 weeks old, were used in these studies. Appropriate doses of imatinib-PK3 particles (containing between 5 μg/kg to 500 μg/kg of imatinib), or an equal quantity of free imatinib, was suspended/dissolved in PBS (200 μL) and was injected intravenously using a 26 G5/8 sterilized needle. One hour later, Con A (15 mg/kg), dissolved in PBS (200 μL), was injected into the intraperitoneal cavity using a 26 G5/8 sterilized needle. Between 4 and 8 mice were used per experimental group. The mice were euthanized 8 h after the Con A injection, by cervical dislocation. Blood was then withdrawn from the heart using a 26 G5/8 sterilized needle, and kept at 4 °C overnight. The serum was isolated by centrifuging at 600g for 10 min and sent to the core facility at the University of Rochester for measurement of ALT levels.

RESULTS AND DISCUSSION

There is currently great interest in developing microparticle-based delivery vehicles that have the biocompatibility and hydrolysis kinetics needed to treat acute inflammatory diseases. Microparticles formulated from the aliphatic polyketol PCADK have excellent biocompatibility and degrade under the acidic conditions of the phagolysosome. However, the slow hydrolysis kinetics of PCADK make it unsuitable for treating acute inflammatory diseases, and therefore strategies for accelerating its hydrolysis kinetics are greatly needed. We previously hypothesized that the slow hydrolysis kinetics of PCADK was due to its hydrophobicity, making the diffusion of water into the polymer matrix the rate-limiting step in ketal hydrolysis (13). This hypothesis was based on the fact that the hydrolysis half-
life of a water-soluble dimethylacetone-based ketal is only 2 min at pH 5.0, which is 3 to 4 orders of magnitude faster than the hydrolysis of the ketal linkages in PCADK (14). Additionally, the hydrolysis kinetics of other water-insoluble polymers, such as polyanhydrides, also scale with their hydrophobicity (10). In this report, the role of hydrophobicity in governing the hydrolysis kinetics of polyketals was investigated. This was accomplished by synthesizing polyketal copolymers of varying hydrophobicity and measuring their hydrolysis kinetics.

Six polyketol copolymers were synthesized in this report (PK1–PK6, Table 1), by copolymerizing 1,4-cyclohexanedimethanol with 1,4-butanediol, 1,5-pentanediol, 1,6-hexanediol, or 1,8-octanediol. The hydrophobicity of these diols is different from that of 1,4-cyclohexanedimethanol (log $P = 1.46$, where $P = $ water/octanol partition coefficient), as evidenced by their respective log $P$ values (Table 2). The synthesis of all the polyketol copolymers was accomplished using the acetal exchange reaction, and was performed on a multigram scale with yields of 50–60% (Figure 1). In general, the introduction of additional diols other than 1,4-cyclohexanediol did not cause any synthetic complications, and procedures developed for the synthesis of PCADK were suitable for the synthesis of all the copolymers. Importantly, all the polyketol copolymers reported in Table 1 were solid, and therefore have the potential for formulation into microparticles.

The hydrolysis kinetics of PK1 to PK6 were measured at the pH values of 4.5 and 7.4 to determine their behavior in the acidic environment of phagolysosomes and in the blood. Figure 2 demonstrates that all the polyketol copolymers (PK1–PK6) undergo acid-catalyzed hydrolysis, and that their hydrolysis kinetics scale with their hydrophilicity. PK1, PK2, and PK3 are copolymers synthesized from 1,4-cyclohexanedimethanol and 1,5-pentanediol. Their hydrophilicity scales with the amount of 1,5-pentanediol incorporated into the copolymer. This is due to the large difference in hydrophilicity between 1,5-pentanediol and 1,4-cyclohexanedimethanol, as evidenced by their respective log $P$ values of 0.27 and 1.46. Figure 2A demonstrates that 1,5-pentanediol significantly accelerates the pH 4.5 hydrolysis kinetics of 1,4-cyclohexanedimethanol-based polyketals. For example, the hydrolysis half-life of PCADK, a homopolyketal synthesized from 1,4-cyclohexanedimethanol, is 24 days at pH 4.5 (13). On the other hand, PK3, a copolymer that incorporates 13 mol % 1,5-pentanediol and 87 mol % 1,4-cyclohexanedimethanol, had a hydrolysis half-life of only 2 days at pH 4.5. Similarly, PK2, another PCADK-derived copolymer, incorporating 7.5 mol % of 1,5-pentanediol, had a hydrolysis half-life of 3 days at pH 4.5, which is faster than PCADK but slower than PK3. PK1, the third copolymer derived from PCADK, incorporating 2 mol % 1,5-pentanediol, was only 30% hydrolyzed after 10 days at pH 4.5, which was expected based on its low incorporation of 1,5-pentanediol.

To determine if diols other than 1,5-pentanediol could similarly influence the hydrolysis kinetics of PCADK-derived copolymers, the hydrolysis kinetics of PK4, PK5, and PK6 were also investigated. These polyketals are PCADK-derived copolymers synthesized from 1,4-cyclohexanedimethanol and either 1,4-butanediol, 1,6-hexanediol, or 1,8-octanediol. Figure 2B,D and Table 2 demonstrate that this set of copolymers also has an inverse relationship between hydrophobicity and hydrolysis kinetics. For example, PK4, a copolymer synthesized from 1,4-cyclohexanedimethanol and 1,4-butanediol, has the

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1 Similar copolymers with higher incorporation of 1,5-pentanediol were also generated; however, those copolymers were viscous liquids, which are not suitable for formulation into microparticles for drug delivery. Therefore, we only focused our hydrolysis analysis on the solid polyketol copolymers, PK1, PK2, and PK3.
fastest hydrolysis kinetics of all the copolyketals, with a hydrolysis half-life of 1 day at pH 4.5. This is predicted based on the more hydrophilic nature of 1,4-butanediol in comparison to the other diols. On the other hand, PK6, a copolymer composed of 1,4-cyclohexanediol and 1,8-octanediol, had a pH 4.5 hydrolysis half-life of 18.6 days. In summary, these data demonstrate that the hydrolysis kinetics of polyketals can be tuned by varying their hydrophilicity and further support the hypothesis that diffusion of water into the polyketals is the rate-determining step governing their hydrolysis. Importantly, the hydrolysis kinetics of all the polyketal copolymers, PK 1–6, were pH-sensitive; in general, they hydrolyzed at least 1 order of magnitude faster at pH 4.5 than at pH 7.4.

We chose PK3 for further investigation as a drug carrier for the treatment of acute inflammatory diseases because of its suitable hydrolysis kinetics and biocompatible degradation products. The copolymer PK4 has faster hydrolysis kinetics than PK3; however, it degrades into 1,4-butanediol, which is converted into γ-hydroxybutyrate in vivo, and subsequently causes toxicity to the central nervous system (15). Microparticles were formulated from PK3, using a solvent evaporation procedure. Figure 4A demonstrates that the size range of PK3 microparticles is between 1 and 5 μm, which is suitable for phagocytosis by macrophages.

In order to determine whether or not PK3 microparticles would have suitable drug-release kinetics for treating acute inflammatory diseases, a release study was conducted on PK3 microparticles which encapsulated the fluorescent dye, rhodamine B. Figure 3 demonstrates that the release half-life of rhodamine B from PK3 microparticles is approximately 6 h at pH 4.5 and 40 h at pH 7.4, which is suitable for treating acute liver failure. The drug-release kinetics of PK3 microparticles is 20 times faster than that of PCADK microparticles, which had a release half-life of 5 days at pH 4.5 and over 15 days at pH 7.4 (data not shown).

PK3 microparticles were used to enhance the delivery of imatinib in treating acute liver failure. Imatinib is a kinase inhibitor that inhibits NF-κB activation and has great potential for treating acute inflammatory diseases (16, 17). The activation of NF-κB in macrophages leads to the production of cytokines and reactive oxygen species, the central causes of tissue damage during acute inflammatory diseases. Although imatinib has shown promise for treating acute inflammatory diseases in mouse models, there are also numerous side effects associated with imatinib, including heart failure and hepatic toxicity (18, 19). PK3 microparticles should enhance the efficacy of imatinib by targeting it to macrophages, thereby increasing its concentration at the target site, and also by reducing the toxic side effects of...
imatinib on the heart and liver. Imatinib was encapsulated into PK3 microparticles through double emulsion procedures. These microparticles were approximately 1.5 μm in size on average, as determined by SEM and DLS, which is suitable for delivering drugs to phagocytic cells such as Kupffer cells (Figure 4B,C). The loading of imatinib in PK3 microparticles was determined to be 0.90 ± 0.10 μg imatinib per 1 mg of particles (n = 3), suggesting that the encapsulation efficiency of imatinib in PK3 microparticles was approximately 0.32%.

The ability of PK3 microparticles to enhance the delivery of imatinib was investigated in mice suffering from Con A-induced acute liver failure. Mice were injected with either imatinib in solution (0.1 μg to 10 μg of imatinib dissolved in 200 μL of saline) or an equivalent amount of imatinib loaded in PK3 microparticles (0.11 mg to 11 mg of imatinib-loaded PK3 microparticles suspended in 200 μL of saline). Acute liver failure was subsequently induced by an intraperitoneal injection of Con A. The severity of liver injury in these mice was determined by measuring the alanine aminotransaminase (ALT) level in their blood, which is a clinical surrogate marker for hepatocyte injury. Figure 5 demonstrates that PK3 microparticles enhanced the treatment efficacy of imatinib in preventing Con A-induced liver damage. For example, a dose of 500 μg/kg of free imatinib resulted in an ALT value of approximately 2000 U, whereas 500 μg/kg of imatinib encapsulated in PK3 microparticles reduced the ALT values to baseline levels of only 50 U. The therapeutic efficacy of 15 μg/kg of imatinib loaded in PK3 microparticles was similar to that of 500 μg/kg of free imatinib. These experiments demonstrate that imatinib-loaded PK3 microparticles significantly enhanced the therapeutic efficacy of imatinib, presumably due to their accumulation in liver macrophages. No noticeable toxicity was observed by injection of empty PK3 microparticles (11 mg suspended in 200 μL of saline), as shown in Figure 5.

CONCLUSIONS

In this report, we demonstrate that the hydrolysis rates of polyketals can be tuned by varying their hydrophilicity. Using this strategy, an aliphatic polyketal copolymer, PK3, was formulated from PK3, which encapsulated the kinase inhibitor, imatinib, and these PK3 microparticles significantly improved the efficacy of imatinib in treating acute inflammatory diseases, given their pH sensitivity, rapid and tunable hydrolysis kinetics, and biocompatible degradation products.

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LITERATURE CITED