Polyketals: A New Family of Polymers For Drug Delivery

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Statement of Purpose: There is currently great interest in developing microparticles that can enhance the delivery of proteins to macrophages. In this presentation, we present a new acid sensitive polymer for drug delivery, poly(cyclohexane-1,4-diyl acetone dimethylene ketal) (PCADK). PCADK is designed to hydrolyze, after phagocytosis by macrophages, in the acidic environment of the phagosome and enhance the intracellular delivery of phagocytosed therapeutics. Other key attributes of PCADK for drug delivery are its well characterized degradation products and straightforward synthesis. PCADK hydrolyzes into 1,4-cyclohexanedimethanol, a compound used in food packaging, and acetone a compound on the FDA GRAS list. PCADK was synthesized using the acetal exchange reaction between 1,4-cyclohexanedimethanol and 2,2-dimethoxypropane, and could be obtained on a multigram scale in one step. The therapeutic enzyme superoxide dismutase (SOD), which scavenges reactive oxygen species, was encapsulated into PCADK-based microparticles using a double emulsion procedure. We anticipate numerous applications of PCADK in drug delivery, based on its acid sensitivity, well characterized degradation products, and straightforward synthesis.

Methods:

Synthesis. PCADK was synthesized in a 50 mL two-necked flask, connected to a short-path distilling head. First, 5.5 mg of re-crystallized *p*-toluenesulfonic acid (0.029 mmol, Aldrich), was added to a 30 mL benzene solution, which contained 1,4-cyclohexanedimethanol (12.98 g, 90.0 mmol, Aldrich). Distilled 2,2-dimethoxypropane (10.94 mL, 90.0 mmol, Aldrich) was added to the benzene solution, initiating the polymerization reaction. Additional doses of 2,2-dimethoxypropane (5 mL) and benzene (25 mL) were subsequently added to the reaction every hour for 6 hours to compensate for 2,2-dimethoxypropane that had been distilled off. The polymer was isolated by precipitation in cold hexane (stored at -20^{o}C) followed by vacuum filtration.

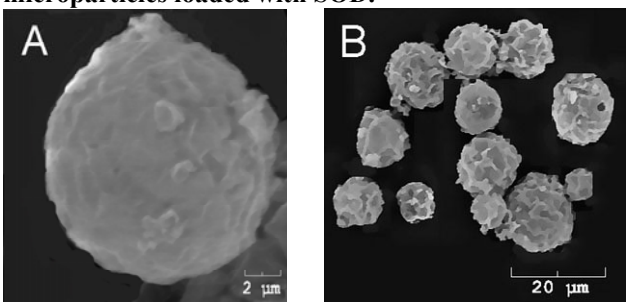
Hydrolysis Kinetics. The hydrolysis rates of PCADK were measured by incubating finely ground PCADK in buffered water at the pHs of 4.5, and 7.4. The samples were then extracted into deuterated chloroform and analyzed for hydrolysis by ^{1}H NMR.

Nanoparticle Formation. SOD was encapsulated into PCADK microparticles using a w/o/w double emulsion procedure. Briefly, a 100 µL aqueous solution of SOD (40 mg/mL) was dispersed by homogenization (21,500 rpm, 30 sec) into 1.0 mL of methylene chloride, containing 125 mg of PCADK, generating a water in oil (w/o) emulsion. This w/o emulsion was then dripped into 5 mL of a 8% (w/v) aqueous polyvinyl alcohol (PVA) solution and was stirred with a homogenizer at 6,000 rpm for 5 min. The resulting w/o/w emulsion was then poured into 25 mL of pH 7.4 buffer, and was stirred for several hours, evaporating the methylene chloride. The resulting particles were isolated by centrifugation and freeze-dried, generating a white solid powder.

Results/Discussion:

PCADK was synthesized with an M_w = 4000, with a yield of 65%. The hydrolysis kinetics of the ketal linkages in PCADK were measured by ^{1}H-NMR and were determined to be pH-sensitive, having a half-life of 24.1 days at pH 4.5 and over 4 years at pH 7.4. The protein encapsulation efficiency of the SOD-PCADK microparticles was 36%, as determined by U.V. absorbance at 280 nm. An SEM image of the SOD-PCADK microparticles, shown in Figure 1, demonstrates that they are 3 to 15 µm in diameter, which is suitable for both intracellular and extracellular delivery.

Figure 1. (A+B) SEM images of PCADK microparticles loaded with SOD.



Conclusions:

In conclusion, we have developed a new acid-sensitive polyketal for drug delivery, PCADK, which is designed to hydrolyze in the acidic environment of the phagosome, and enhance the intracellular delivery of phagocytosed therapeutics. Key attributes of PCADK are its well characterized degradation products and straightforward synthesis.

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