Polyketal Copolymers: Acid Sensitive Biodegradable Polymers with Tunable Hydrolysis Rates for Drug Delivery

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Statement of Purpose: Biodegradable polymers that degrade into biocompatible products have attracted much attention in the field of drug delivery and biomaterials. Drug delivery systems based on biodegradable polymers offer numerous advantages such as controlled rates of release, selective release of drugs to areas of interest, and assisting cell up-take of drugs. For drug delivery systems to phagocytic cells such as macrophages, acid-sensitive polymers offer one major advantage over biodegradable polymers that are not acid-sensitive. Drug delivery systems based on acid-sensitive polymers can take advantage of the lower pH environment inside phagosomes and selectively release drugs to cells upon phagocytosis. In this presentation, we demonstrate that an acetal exchange reaction can be used to generate an array of polyketal copolymers from a wide variety of diols, including diols with well characterized toxicity profiles. These polyketal copolymers degrade under acidic conditions with tunable hydrolysis rates and generates neutral degradation products, diols and acetone. Nano and micro sized particles can be formulated using these polyketal copolymers to load hydrophilic biological agents via double emulsion processes.

Methods: The polyketal copolymers were synthesized via step growth polymerization. Briefly the diols were added to distilled benzene along with equal molar of 2,2-dimethoxypropane and trace amount of p-toluenesulfonic acid, and temperature was set at 100^{o}C. Additional doses of 2,2-dimethoxypropane and benzene were subsequently added to the reaction every hour for 6 hours to compensate for 2,2-dimethoxypropane and benzene that had been distilled off. After 8 hours, the reaction was stopped by lowering the reaction temperature to room temperature. Subsequently, the reaction mixture was poured into cold hexanes and stored in -20^{o}C. After 12 h, either a white or yellow solid precipitate was isolated and dried under vacuum for 24 h. The polymers were characterized by ^{1}H NMR and GPC to confirm molecular weight and chemical structure. Hydrolysis of polyketal copolymers were determined by ^{1}H NMR.

Particles based on polyketal copolymers were formulated using a water/oil/water emulsion method to load superoxide dismutase (SOD) labeled with FITC. CH_2Cl_2 was used as the organic phase, and 5% PVA solution was used as the aqueous phase in the emulsion process. Particles were characterized by SEM and incubated with TIB186 macrophage cells for 1 hour for cell uptake study.

Results/Discussion: The hydrolysis of polyketal copolymers were estimated under various pH conditions. Figure 1 suggests that hydrolysis rates of polyketal copolymers at pH 4.5 were correlated with the hydrophilicity of the monomers used to synthesize the copolymer. Significantly, polyketal copolymers did not undergo substantial hydrolysis within the time scale of the experiments at pH 7.4, which is physiological pH.

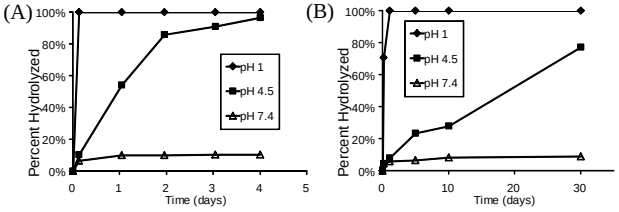

Figure 1: (A) Hydrolysis profiles of 1,4-cyclohexanedimathanol and 1,4-butandiol copolymer. (B) Hydrolysis profiles of 1,4-cyclohexanedimathanol and1,8-octandiol copolymer.

Polyketal copolymers were used to formulate nano and micro sized particles loaded with FITC-SOD. These particles were incubated with macrophage cells. Figure 2B shows that the fluorescence activity was occurring inside the macrophage cells, indicating that FITC-SOD particles were effectively taken up by macrophage cells. These results suggest that proteins can be effectively delivered to phagocytic cells using a polyketal copolymer based system. We believe that polyketal copolymers have great promise for the intracellular delivery of water soluble proteins, which normally are poorly taken up by cells because of their inability to cross the cell membrane.

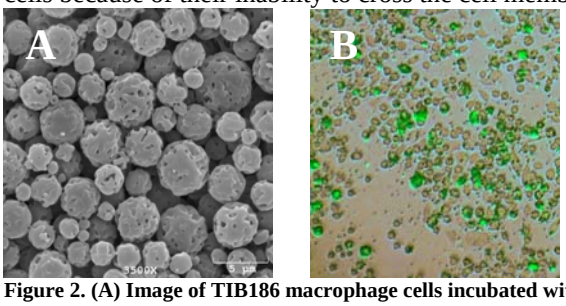

Figure 2. (A) Image of TIB186 macrophage cells incubated with Figure 2: (A). SEM image of FITC-SOD loaded particles.(B) Overlay image of TIB186 macrophage cells incubated with FITC-SOD particles from 10X phase contrast microscope and 10X fluorescence microscope.

Conclusions: Polyketals copolymers offer numerous advantages for intracellular drug delivery to phagocytic cells because polyketal copolymers have tunable hydrolysis rates at the endosomal pH of phagocytic cells and very low level of hydrolysis at neutral pH. The degradation products of polyketal copolymers are low molecular weight, neutral compounds that do not affect acid-labile compounds and can be more easily removed from cells. Preliminary results show that a protein SOD can be loaded in polyketal copolymer based particles, which can then be effectively taken up by macrophage cells. These properties demonstrate great promises for polyketal copolymers to be used in intracellular drug delivery systems for the delivery of proteins and nucleotides.