Polyketals: a New Drug Delivery Platform for Treating Acute Liver Failure

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Statement of Purpose: Acute inflammatory diseases such as acute liver failure cause millions of death each year, and effective treatments are greatly needed.(*1*) Pro-inflammatory cytokines secreted by liver macrophages (Kupffer cells) play a central role in mediating acute liver failure, and drug delivery vehicles that can target therapeutics to Kupffer cells have great clinical potential.(*2*) A key drug delivery requirement for the treatment of acute liver failure is rapid release of drugs, ideally within the order of a few hours. This is because at the time of patient diagnosis, significant tissue damage has already occurred, and liver function is rapidly deteriorating. It has been challenging to develop clinically acceptable drug delivery vehicles that can target therapeutics to Kupffer cells and release them rapidly. Microparticles, formulated from biodegradable polymers, have a major advantage for treating acute liver failure because they can passively target therapeutics to Kupffer cells. However, existing biomaterials are not suitable for the treatment of acute liver failure because of their slow hydrolysis kinetics and acidic degradation products. In this presentation, we demonstrate that we have developed a polyketal copolyer, termed poly(cyclohexane-1,4-diyl acetone dimethylene ketal-co-1,5-pentane-acetone dimethylene ketal) (PK3), which has the suitable hydrolysis kinetics for treating acute liver failure. Microparticles based on PK3 also have suitable drug release kinetics to target therapeutic agents to Kupffer cells and improve the treatment of acute liver failure.

Methods: For the release study, rhodamine B was encapsulated in PK3 microparticles using single emulsion procedures. Rhodamine B-loaded microparticles was suspended in pH 4.5 and pH 7.4 buffer solutions. The suspensions were kept at 37^{o}C. At specific time points, 100 µL of the suspensions was centrifuged to remove unhydrolyzed particles the supernatant was then analyzed by a spectrofluorophotometer to quantify the relative concentration of rhodamine B released form the microparticles (excitation wavelength = 556 nm, emission wavelength = 573 nm). For animal studies, mice were injected intravenously with either imatinib or imatinib in PK3 microparticles, acute liver failure was then induced by intraperitoneal injection of Con A (15 mg/kg). 8 hours later, ALT levels in the blood were analyzed.

Results: As shown in Figure 1, the release half-life of PK3 microparticles is approximately 6 hours at pH 4.5 and 40 hours at pH 7.4; therefore PK3 microparticles have suitable drug-release kinetics for treating acute liver failure. The size range of PK3 microparticles is between 1 to 5 microns, which are suitable for phagocytosis by Kupffer cells.

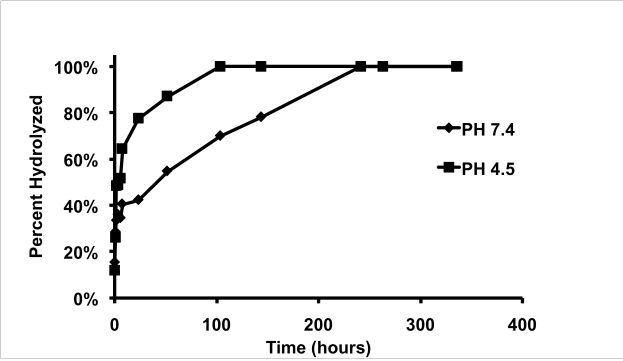

Figure 1. Release kinetics of PK3-microparticles

The anti-inflammatory drug, imatinib, was encapsulated into PK3 microparticles. Figure 2 demonstrates demonstrate that imatinib-loaded PK3 microparticles significantly enhanced the therapeutic efficacy of imatinib, presumably due to their accumulation in liver macrophages.

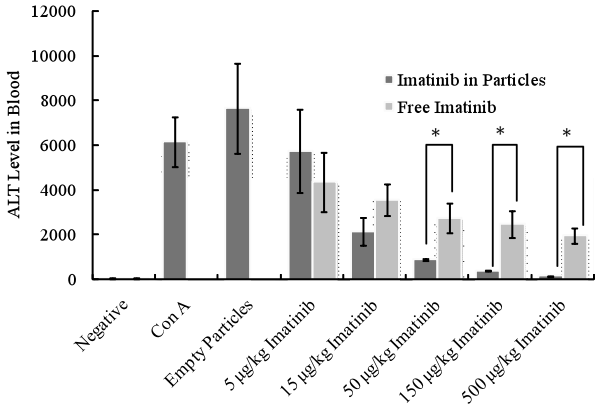

Figure 2. PK3 microparticles improve the efficacy of imatinib in treating acute liver failure in mice. * indicates statistical significance ($P < 0.05$, n = 4 to 8).

Based on these findings, we anticipate numerous applications of polyketals for treating acute inflammatory diseases, given their pH sensitivity, rapid hydrolysis kinetics, and biocompatible degradation products.

References:

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(2) Schumann, J., et al., *Importance of Kupffer cells for T-cell-dependent liver injury in mice.* Am J Pathol, 2000. **157**(5): p. 1671-83.