Drug Release Profile of Nanoparticle-Hydrogel Formulations for Sustained Delivery of Tacrolimus

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Purpose: Non-adherence to oral Tacrolimus (TAC), a common immunosuppressant used following kidney transplants, in adolescents and young adults is the primary reason for kidney rejection. Hydrogels are often employed as sustained delivery vehicles for hydrophobic drugs. Previously, we synthesized polyvalerolactone-based hydrogel capable of forming biodegradable gel at body temperature upon subcutaneous injection. In this study, we have prepared and evaluated a TAC-loaded nanoparticle-hydrogel formulation intended for weekly dosing in vivo model as an initial step to develop a hydrogel-based sustained delivery system for tacrolimus.

Method: Various TAC nanoparticles were prepared with different polymers using solvent evaporation method. The most stable TAC nanoparticle was used to formulate the polyethylene glycol-b-polycapralactone hydrogel for injection. Eight groups (n=32, 4/group) of Swiss-Webster mice were injected with the nanoparticle-hydrogel and another eight groups with TAC-hydrogel formulation. Whole blood was collected by cardiac puncture and analyzed by LC-MS/MS for TAC and creatinine concentrations. Weights, grooming and feeding behaviors were monitored on a daily basis after injection.

Results: At polymer concentration of 5 mg/mL, PEG5k-b-PCL10k nanoparticles loaded with TAC were able to solubilize at 949±1.0 µg/mL. The nanoparticles were stable for 24 h at 25°C with more than 98% drug was retained in solution and minimal change in size. TAC release profile from PEG5k-b-PCL10k shows a significantly smaller burst effect than PEG5k-b-PLA10k. Tacrolimus released from the nanoparticle hydrogel formulation maintained a concentration in the range of 5 to 15 ng/mL up to 7 days. The Cmax for TAC-nanoparticle hydrogel was significantly lower than that of TAC hydrogel (16.5±3 ng/mL vs 25±3 ng/mL). Creatinine level remained within the 1 – 1.5 µg/mL range for the TAC-nanoparticle hydrogel formulation. Neither significant drop in weight nor change in animal behaviors was observed in both formulations.

Conclusion: TAC-nanoparticle hydrogel formulation maintained clinically relevant TAC concentrations up to 7 days. Overall, both formulations showed no significant toxicity in terms of weight loss or change in animal behavior. PVL-based TAC-nanoparticle hydrogel formulation has a potential as a sustained delivery system for the prevention of graft rejection.

References: