Bone targeted antibiotic delivery with functionalized poly(ε-caprolactone) microparticles

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Osteomyelitis, the medical term for infection of the bone, is a serious complication with high (up to 30%) incidence in open bone fractures. Current treatment strategies involve a debridement of the infected tissue, followed by a combined therapy with systemic antibiotics and the implantation of antibiotic releasing biomaterials. The success rate of such therapies is still insufficient, with 30% of the patients showing recurrence of the infection after 12 months. The impaired blood supply to the tissue surrounding the infection prevents optimal supply of systemic antibiotics, and many antibiotic loaded biomaterials show either too fast or insufficient drug release.

In this study, we aim to develop a biodegradable poly(ε-caprolactone) (PCL) microparticulate delivery system for antibiotics, to be used locally at the site of infection. Hydrophobic Gentamicin (GM-AOT) or Ciprofloxacin (CF) was internalized in the microparticles that were fabricated with O/W emulsions. The surfactant poly(vinyl alcohol) (PVA) was modified with ring-opened succinic anhydride to endow carboxylic acid functional groups on the surface of the antibiotic loaded microspheres. The bone binding oligomer of Aspartic acid (ASP) was grafted on the surface of the microparticles through carbodiimide conjugation chemistry. The functionalized microparticles were assessed in terms of antibiotic release profile and affinity to calcified materials.

PVA surfactants were successfully carboxylated as was assessed by proton nuclear magnetic resonance (^{1}H-NMR) measurements. Grafting of ASP was analyzed by DOSY-NMR. The complete GM-AOT load was gradually released over a two-week period, while ciprofloxacin release plateaued at approximately 65% of total drug load. Affinity of ASP functionalized microspheres increased 3.6-fold compared to non-functionalized microspheres, indicating that a high antibiotic release at the bone interface can be expected during further testing. Antimicrobial efficacies of bone-bound microparticles were proven by zone of inhibition experiments with microparticle-laden hydroxyapatite granules.

Allowing for antibiotic release at the bony interface, it is expected that ASP functionalized PCL antibiotic carriers can improve osteomyelitis treatment.