Efficacy, release profile, and degradation behaviour of PDLLA + Gentamicin Sulphate coating on Ti-6Al-7Nb alloy in PBS

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Statement of Purpose: Fully resorbable coatings based on poly(D,L-lactide) (PDLLA) and Gentamicin Sulphate were previously shown to be effective in preventing colonisation of the implant surface in an infection model in the rat tibia [1].
In the present work, we investigate the degradation behaviour of the coating in PBS at 37°C over a time period of 32 weeks. The efficacy of the released antibiotic is characterized in zone of inhibition testing against *Staphylococcus aureus*.

Materials and methods:
Samples of Ti-6Al-7Nb alloy (TAN) of 5 mm diameter and 150 mm length were coated with a PDLLA coating containing Gentamicin Sulphate by using a dip coating process.
Average coating mass was 16.4 mg, corresponding to 1.1±0.3 mg/cm^2, as determined gravimetrically. The average content of Gentamicin Sulphate was 0.19±0.05 mg/cm^2, determined by FMOC derivatisation and HPLC. All samples were sterilised by γ-irradiation at 29kGy. Samples were soaked in phosphate buffered saline at 37°C and extracted at the following time points: 2, 4, 8, 12, 16, 24 and 32 weeks. At each time point visual evaluation of degradation, molecular weight distribution by gel permeation chromatography (GPC), and surface analysis by scanning electron microscopy were performed. Efficacy of the coating was investigated in a zone of inhibition test against *Staphylococcus aureus*. [2] Coated samples were exposed to fresh cultures on agar plates every 48 hours, inhibitory zone diameter was measured. A reference curve was recorded in parallel to assess the MIC level as a function of zone diameter.
Results: Degradation of polymer, GPC: Over the first 12 weeks a gradual decrease in the weight average molecular weight M_w was observed. Between 12 and 16 weeks an increased degradation of the polymer occurs, M_w dropping from 18'100 D to 9'450 D, concurrent with visible whitening of the coating. From 16 to 32 weeks degradation occurs at an increased rate. After 32 weeks hardly any residual coating can be found, M_w has dropped to 3'100 D, with a very clear peak at around 250 D in the chromatogram, which may point to an increased content of lactic acid oligomers.
SEM surface analysis: After 2 weeks of soaking pores are recognizable in the surface of the coating, indicating the dissolution of the antibiotic particles contained in the coating; at the subsequent time points an increased degradation can be seen starting from the spots where gentamicin sulphate was contained (Fig 1).
Zone of inhibition: A detectable zone of inhibition with concentrations of antibiotic above MIC for *S. aureus* was detected for up to 32 days of culturing. The release profile follows a distinct burst release (Fig 2).

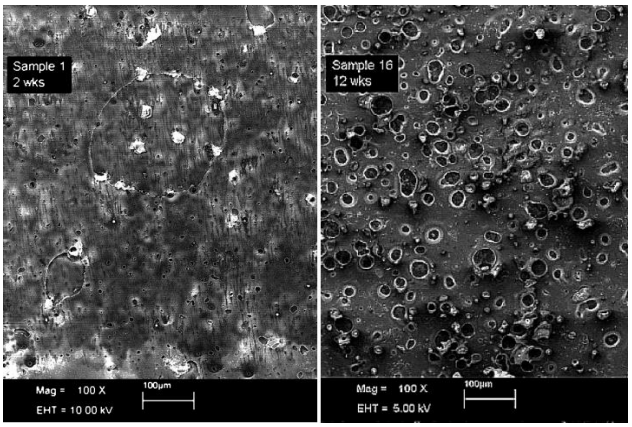

Figure 1: SEM image of the coating surface after 2 (left) and 12 weeks (right) of soaking in PBS at 37°C.

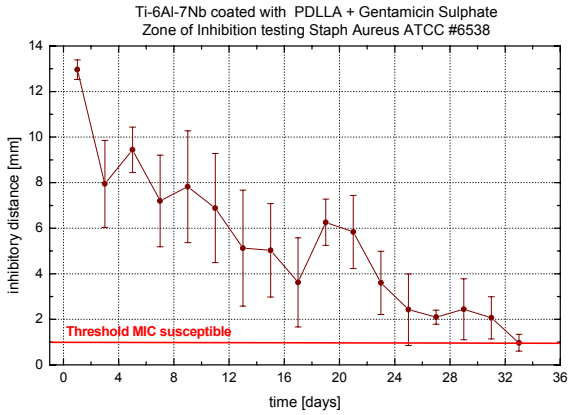

Figure 2: Zone of Inhibition test: activity of PDLLA+Gentamicin sulfate coating against *S. aureus*.

Conclusions: The investigated coating of poly(D,L-lactide) and Gentamcin sulphate is fully resorbable, degradation occurs through hydrolytic scission of the chains. The release of the antibiotic occurs in a distinct burst release as could be expected for this highly hydrophilic substance. The amount of released antibiotic and the burst release profile indicate that this coating formulation is appropriate to confront and inhibit initial surface colonization of an orthopedic implant by bacteria in the time immediately following implantation. The subsequent complete resorption of the coating guarantees that no residual antibiotics at low concentrations are left, which may cause a potential risk of selecting or breeding antibiotic resistant strains.

References: Lucke M. et al, *Bone* (2005) 32(5): 521-531.
Murray P. et al; *Manual of Clinical Microbiology*, Ch. 13; 6th ed. 1995; ASM, Washington DC.