

Controlled release of tetracycline from biodegradable and biocompatible tricalciumphosphate bone substitute material

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INTRODUCTION: Local antibiotic delivery systems are promising alternatives to the systemic antibiotic treatment in the prevention of bone infections in orthopaedic surgery [1]. Therefore, we developed a tetracycline (Tet)-laden bone substitute material based on tricalciumphosphate (TCP) granules. Release kinetics were modulated by using different types of biodegradable polymers to incorporate Tet. *In vitro* evaluation showed a good biocompatibility of the device and maintenance of the stability and bioactivity of released Tet.

METHODS: TCP granules (calc-i-ossTM) were coated with poly(lactide) and poly(lactide-co-glycolide) (PL(G)A) incorporating tetracycline (Tet). To modulate release kinetics six different formulations were prepared (A – F). Tet loading of TCP granules was determined by a modified HPLC method as previously described [2]. The thickness of the PL(G)A coating layer was analysed by using a scanning electron microscope. Tet release kinetics were investigated *in vitro* by incubating 100 mg of TCP granules (n = 3) in 1 ml phosphate buffer at 37°C during 67 days and Tet concentration was analysed by HPLC. A reporter cell line (CHO XM 111.10) with a Tet-responsive SEAP expression vector [3] was used to measure the biological activity of released Tet. Cellular biocompatibility testing was performed according to ISO 10993-5 guidelines using an osteoblast cell line (MG-63).

RESULTS: TCP granules contained between 22.4 and 29.2 µg Tet per mg implant material.

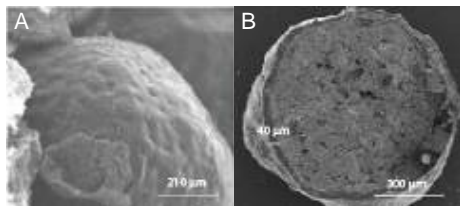


Fig. 1: Surface morphology (left) and cross section (right) of TCP composites incorporating Tet within the polymer coating layer.

In vitro release studies showed that Tet release was prolonged over a time period of 67 days and that release kinetics were dependent on the type of used polymer coating (Fig. 2).

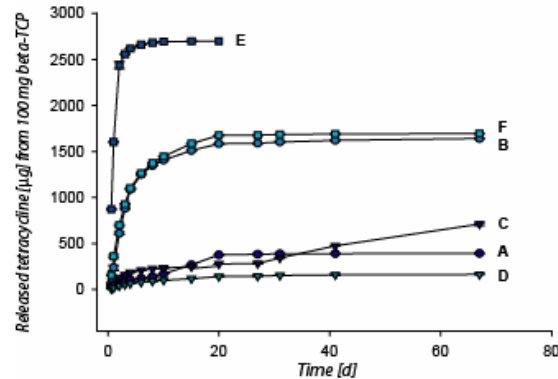


Fig. 2: *In vitro* tetracycline release from six different TCP composite formulations (A-F).

All formulations were able to induce a biological response as demonstrated by the reduction of SEAP expression in the genetically modified CHO cell line (Tab. 1). *In vitro* biocompatibility analysis showed no reduction in cellular viability.

Table 1. Alkaline phosphatase activity in response to released tetracycline from TCP granules.

	SEAP activity [µM/min] after 24 h	± SD
Negative control (without Tet)	300.0	± 22
Positive control (20 µg/ml Tet)	76.8	± 8.5
Formulation A-F	70.4 – 82.0	± 6.2

DISCUSSION & CONCLUSIONS: The developed local antibiotic delivery system allows sustained Tet release with different kinetics while providing osteoconductive properties. *In vivo* evaluation of this bone substitute material is currently under investigation.

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