

BISPHOSPHONATE BASED COATINGS FOR HARD TISSUE IMPLANTS



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INTRODUCTION

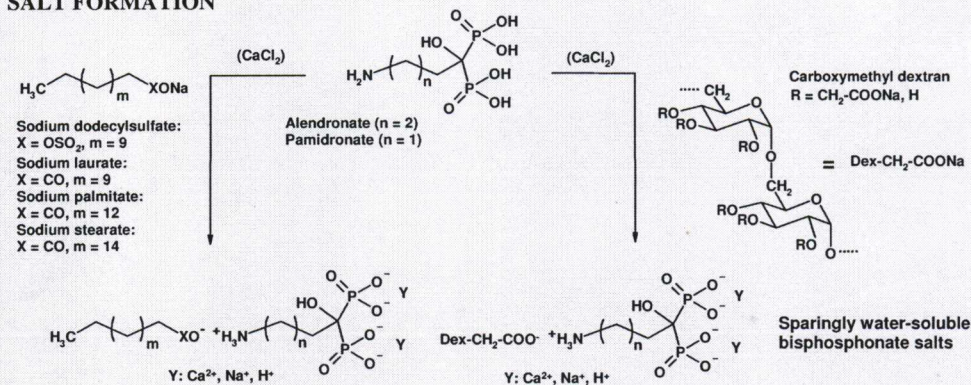
The rapid mechanical fixation of a hard tissue implant based on a solid osteointegration is of crucial importance for its functionality and life-time in the body.

A promising approach to promote implant osteointegration represents the modification of implant surfaces with bioactive agents. Recently, it was shown that the local delivery of bisphosphonates, which are known to inhibit bone resorption, increases the mechanical fixation of metallic implants [1,2]. Unfortunately, because of its high water solubility, the release of physically immobilized bisphosphonates is only controlled by diffusion and a sustained effect is hard to achieve.

In this context the aim of our work was the preparation of sparingly water-soluble bisphosphonate salts which can be used as coating materials for metallic implants generating a sustained release effect.

RESULTS & DISCUSSION

SALT FORMATION



MATERIALS & METHODS

MATERIALS

Salt exchange reactions were performed using alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonate) and pamidronate (3-amino-1-hydroxypropylidene-1,1-bisphosphonate) as bisphosphonate components and sodium salts of various long-chain fatty acids (stearic, lauric, palmitic acid), dodecyl sulfonic acid (SDS) as well as the sodium salt of carboxymethyl dextran (CMD, degree of carboxymethylation (DS) = 0.7).

SALT FORMATION

Aqueous solutions of the components were mixed and stirred at room temperature or 80 °C for 18 h. Aqueous 1 molar CaCl₂ solution was used to test the influence of calcium ions on the salt formation. Formed precipitates were isolated by centrifugation, washed with distilled water and dried. Conventional analytical methods (FT-IR spectroscopy, elemental analysis) were used to determine the chemical composition of the products.

COATING PROCEDURE

For coating experiments homogeneous suspensions of the formed sparingly water-soluble bisphosphonate salts were prepared in a suitable solvent (e. g. chloroform, methanol, ethanol). Coating of titanium samples (cp, grade 4, sandblasted and acid etched) was performed by spray coating.

ANALYTICS

In vitro release studies were conducted in physiological NaCl solution at 37°C. Drug concentrations were determined UV-spectroscopically after derivatization of the released bisphosphonate with o-phthalaldehyde.

VARIATION OF BISPHOSPHONATE SALT COMPOSITION

• Alendronate (AL) + fatty acid (FA)

FATTY ACID	MOLAR RATIO AL : FA	TEMPERATURE [°C]	YIELD [%]
Stearic acid	1 : 1	80	32
Lauric acid	1 : 1	r. t.	32
Palmitic acid	1 : 1	80	12
SDS	1 : 1 (+ Ca ²⁺)	r. t.	88

• Pamidronate + fatty acid (molar ratio 1 : 1 (+Ca²⁺))

FATTY ACID	TEMPERATURE [°C]	YIELD [%]
Stearic acid	80	69
Lauric acid	r. t.	64
Palmitic acid	80	45
SDS	r. t.	61

• Alendronate + stearic acid + Ca²⁺

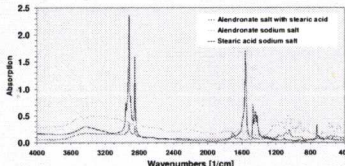
MOLAR RATIO BIS : FA : Ca ²⁺	YIELD [%]	AL CONTENT [%]
1 : 1 : 0.2	39	12.7
1 : 1 : 0.5	56	27.9
1 : 1 : 1	81	55.4
1 : 1 : 2	83	25.9

• Alendronate + CMD (room temperature):

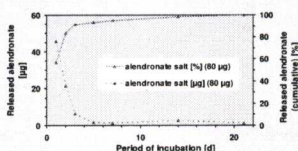
MOLAR RATIO BIS : CMD	YIELD [%]
2 : 1 (+ Ca ²⁺)	57
1 : 1 (+ Ca ²⁺)	44
1 : 2 (+ Ca ²⁺)	23

CHARACTERIZATION

• FT-IR spectroscopy

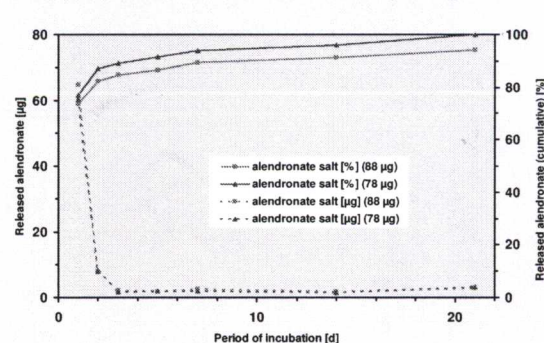


• Release of alendronate from stearate salts



IN VITRO RELEASE STUDIES

• Release of alendronate from SDS salt-containing coatings



CONCLUSIONS

New sparingly water-soluble bisphosphonate salts have been prepared and tested as degradable coating systems for titanium implants. Using the developed salts, thin coatings with good substrate adhesion on titanium implant surfaces can be prepared by simple spray-coating technique without adding film-forming additives. The alendronate containing coatings show a retarded release of the bisphosphonate over several days.

Based on these results, the new alendronate salts seem to represent promising candidates for the generation of bioactive implant coatings modulating the local and controllable availability of bisphosphonates within the bone-implant interface. First results of an *in vivo* study using a sheep model have shown that the developed bisphosphonate coating has the potential to enhance peri-implant bone healing.

References

- P. Tengvall, B. Skoglund, A. Askendal, P. Aspenberg (2004) *Biomaterials* 25:2133-38.
- H. Kajiwara, T. Yamaza, M. Yoshinari, et al. (2005) *Biomaterials* 26: 581-87.