Drug release from gelatin-calcium titanate composite formed on Ti-6Al-4V alloy

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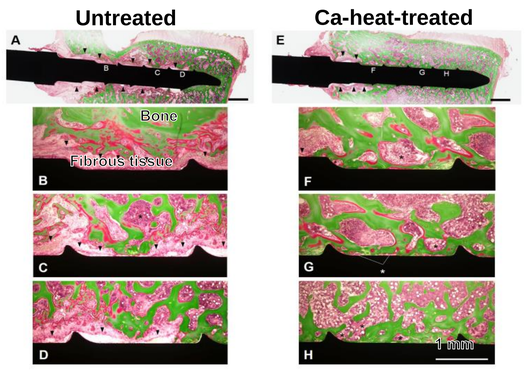
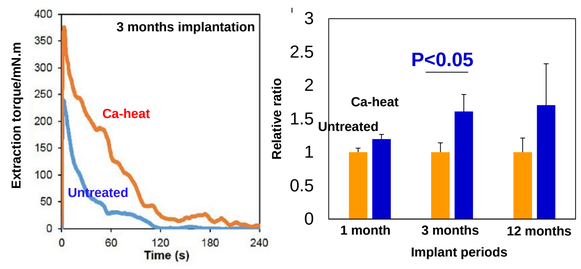
Background

Ti-6Al-4V alloy has been widely used for orthopedic and dental fields owing to its high mechanical strength and biocompatibility. The alloy, however, is insufficient in bone-bonding capacity and its implant often causes loosening. Osteoporosis increases with aging of the population, and drugs of bisphosphonate (BS) such as alendronate and minodronate (MA) are used for the medical treatment. **Reliable and multifunctional implants showing both of bone bonding and drug releasing functions are desired.**



Histology of untreated and Ca-heat-treated pedicle screw in lumber of beagle dogs at 3-months post-surgery.

Ti-6Al-4V pedicle screw (PS) subjected to Ca-heat treatment tightly bonded to bone without intervention of fibrous tissue [1].

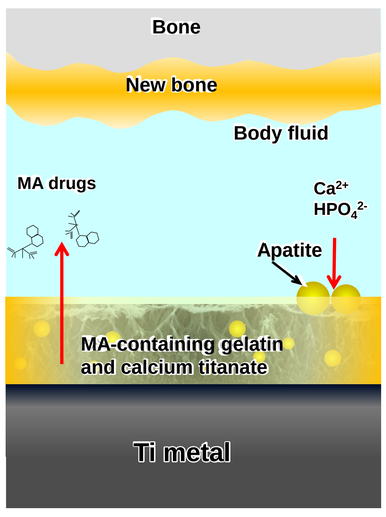


Extraction torque curve and relative ratio of its peak top values post surgery of untreated and Ca-heat-treated pedicle screw in lumber of beagle dogs .

Extraction torque curve of Ca-heat-treated PS maintained higher values than untreated PS throughout the recording periods. Significant difference in averaged torque was observed at 3 months implantation period [1].

[1] Akeda K, et al. PloS ONE. 2018;13(5):e0196766.

Concept

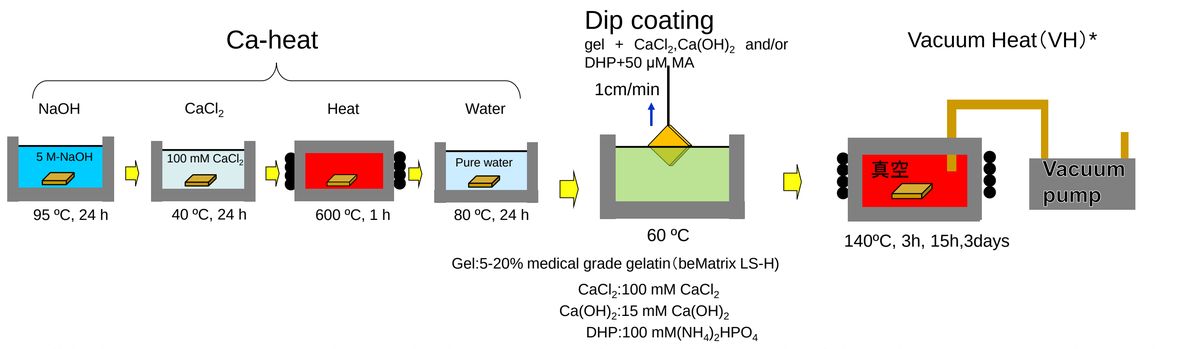


Calcium titanate layer formed by Ca-heat treatment exhibits osteoconductivity owing to its apatite formation capability as well as high scratch resistance [1]. Meanwhile drug containing hydrogel exhibits osteoinductivity although its scratch resistance is usually poor.

In this study, we developed novel organic-inorganic composite layer consist of MA-containing gelatin and calcium titanate on Ti-6Al-4V alloy to provide osteoconductivity and osteoinductivity as well as high scratch resistance. Its apatite formation, scratch resistance and dissolution rate of gelatin are evaluated.

[1] Akeda K, et al. PloS ONE. 2018;13(5):e0196766.

Materials and Methods



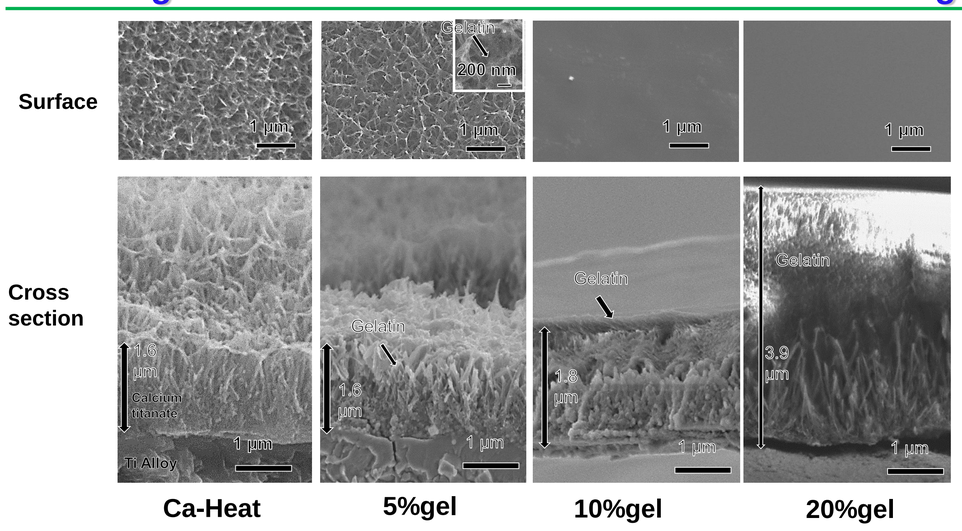
Modified Ca-heat treatment for producing MA-containing gelatin and calcium titanate composite on the Ti-6Al-4V surface.

The composite of MA-containing gelatin and calcium titanate was produced on Ti-6Al-4V by Ca-heat treatment and subsequent dip coating. Vacuum heat treatment that promotes cross-link of gelatin [2] was examined after the dip coating to suppress the initial degradation rate of the gelatin.

[2] Tsujimoto et al, J Biomater Mater Res Part B: Appl Biomater, 2015; 103B: 1511-1518.

Results

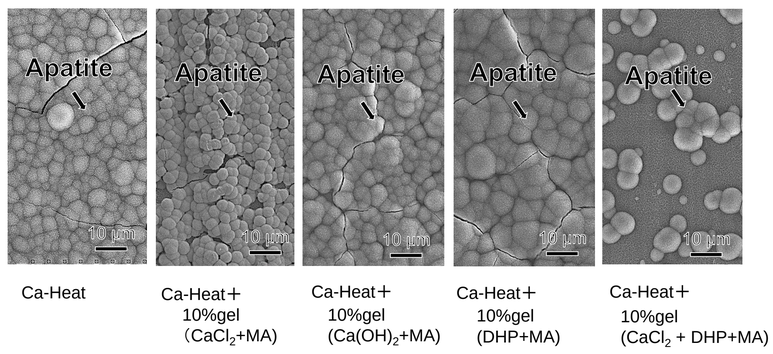
Effect of gelatin concentration on the thickness of coating layer



SEM images of surfaces and cross sections of Ti-6Al-4V alloy subjected to Ca-heat treatment and subsequently dip coating with 5, 10 and 20 % gelation solution.

Three dimensional network structure composed of calcium titanate with 1.8 μm thickness was produced on Ti-6Al-4V alloy by the Ca-heat treatment. When the samples were subjected to DC treatment using 5% gelatin, only a partial surface modification with gelatin was observed. In contrast, sample surface was fully covered with gelatin when 10 or 20% gelatin was used. Cross-sectional observation revealed that gelatin penetrated into the network structure to be integrated with the calcium titanate to form the organic-inorganic composite layer.

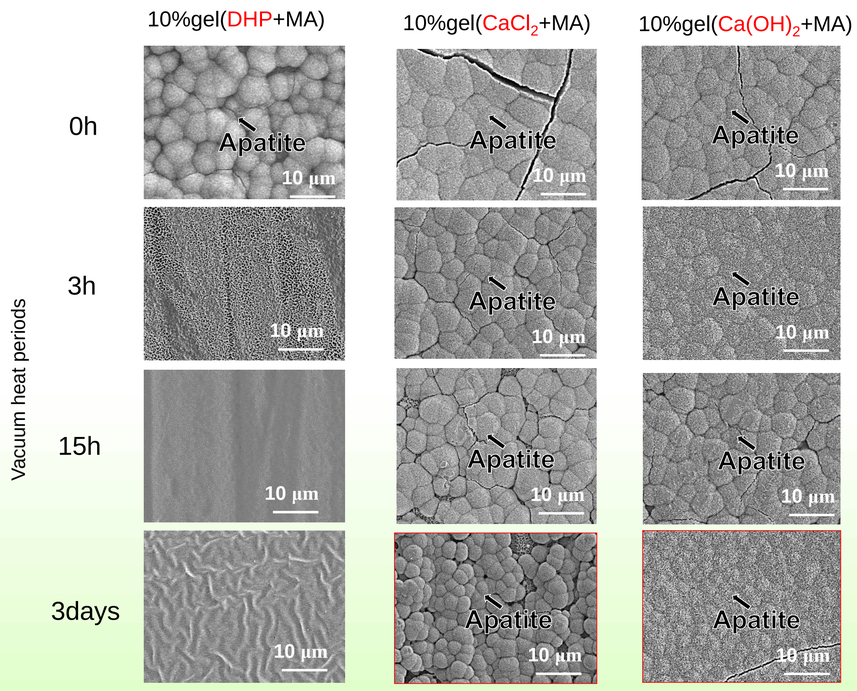
Apatite formation: effect of additives in a coating layer



SEM images of surfaces of Ti-6Al-4V soaked in SBF for 7 days with or without dip coating including various additives following Ca-heat treatment.

Apatite fully covered the sample surfaces within 7 days in SBF only if the additives of $CaCl_2$, $Ca(OH)_2$ or $(NH_4)_2HPO_4$ was used solely.

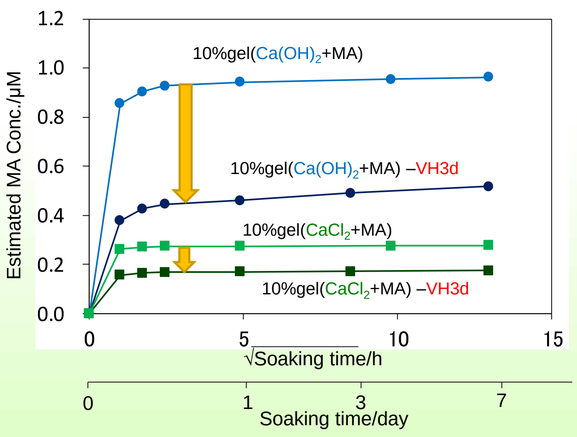
Apatite formation: effect of vacuum heat treatment



SEM images of surfaces of Ti-6Al-4V soaked in SBF for 7 days with or without vacuum heating following Ca-heat and dip coating.

Apatite formation of the composite layer maintained even after the vacuum heat treatment for 3 days when $CaCl_2$ or $Ca(OH)_2$ was used as the additives.

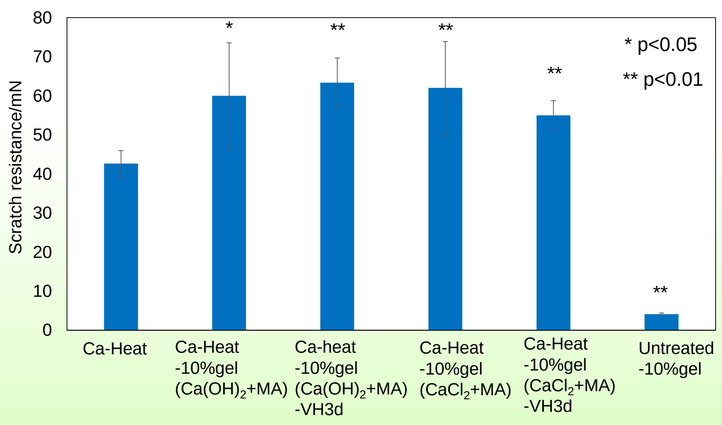
Degradation rate of gelatin layer



Degradation rate of gelatin from the composite layer on Ti-6Al-4V. MA concentration was estimated from the released Ca^{2+} ions into saline measured by ICP.

Degradation rate of gelatin in the composite layer at an initial soaking period was significantly suppressed by vacuum heat treatment. Estimated MA concentration was above 0.1 μM that is effective for suppressing bone resorption.

Scratch resistance

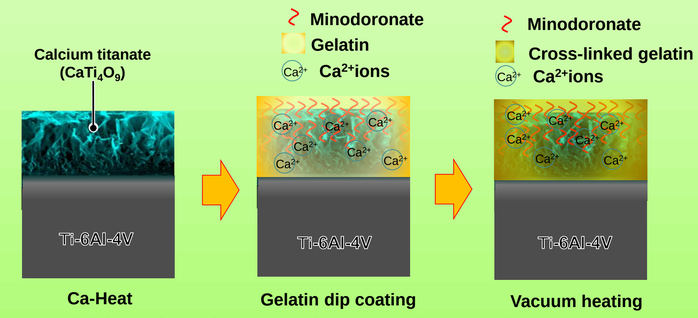


Scratch resistance of Ti-6Al-4V alloy subjected to Ca-heat treatment followed by dip coating using 10 % gelatin containing MA and vacuum heating for 3 days.

Scratch resistance of Ca-heat sample showed about 40 mN. This increased by the subsequent dip coating up to about 60 mN regardless the kinds of additives and the post vacuum heat treatment. These values were significantly higher than that on the sample subjected to dip coating without Ca-heat treatment.

Summary

Novel organic-inorganic composite of MA-containing gelatin and calcium titanate was produced on Ti-6Al-4V alloy. The treated alloy exhibited high scratch resistance, apatite formation and MA releasing capacity, and thus will be useful for the treatment of osteoporosis bone.



Schematic illustration of fabrication of MA-containing gelatin and calcium titanate composite in the present study